Original Research Article

To evaluate therapeutic efficacy, tolerability and safety of "Flaxseed oil" containing omega-3 essential fatty acid (ω-3-EFA) in patients of Rheumatoid arthritis (RA) – A Randomized, Placebo controlled, Single blinded study

Dinesh J Vyas[1], Satish Kumar Gupta[2], Swati Jangir[3], Atul Rajpara[2*]

[1]Associate Professor, Department of Pharmacology, American International Institute of Medical Science, Udaipur, Rajasthan, India
[2]Assistant Professor, Department of Pharmacology, American International Institute of Medical Science, Udaipur, Rajasthan, India
[3]Assistant Professor, Department of Pharmacology, American International Institute of Medical science, Udaipur, Rajasthan, India

Received: 10-10-2020 / Revised: 22-11-2020 / Accepted: 02-12-2020

Abstract

Introduction: Rheumatoid arthritis is a chronic and progressive illness that has the potential to cause joint destruction and functional disability. Early medical intervention has been shown to improve outcomes and function and stops damage to joints. Omega 3 fatty acids are shown to have anti-inflammatory action.**Objectives:** The present study was planned to evaluate efficacy, tolerability and safety of flaxseed oil supplementation in in patients of Rheumatoid arthritis.**Material and methods:** The study was randomized, Placebo controlled, single blinded study at Department of Orthopaedics of a tertiary care teaching hospital and private orthopaedic hospital in Gujarat. Enrolled patients received flaxseed oil or placebo over a period of six weeks. Clinical features, laboratory investigations and adverse reactions were recorded and compared with baseline values.**Results:** Flaxseed oil supplementation was associated with a greater improvement in symptoms and joint function after six weeks of treatment as compared to placebo group. Also, tolerability of flaxseed oil was similar to the placebo group.**Conclusion:** Flaxseed oil supplementation may have a beneficial effect in patients of Rheumatoid arthritis. Further large-scale studies are recommended to evaluate the role of flaxseed oil supplementation in Rheumatoid Arthritis.

Keywords: Essential fatty acids (EFAs), flaxseed oil, Rheumatoid arthritis.

Introduction

It is the type of fats and oils and not the amount of fats and oils that we eat which causes the problem and also correlated directly to the rise of epidemic of degenerative diseases [1-3]. At present, majority of diets consumed globally contain significantly higher levels of omega-6 fatty acids, which leads to increased levels of long chain n-6 polyunsaturated fatty acids (ω-6 PUFAs) and decreased levels of long chain n-3 polyunsaturated fatty acids (ω-3 PUFAs) in the body. This has been associated with elevated levels of pro-inflammatory eicosanoids and cytokines which facilitates degenerative inflammatory and autoimmune diseases including rheumatoid-arthritis (RA) [4-8]. Globally, the incidence of rheumatoid arthritis (RA) is increasing day by day and is expected to affect more than 60 million people across the world by the end of 2020.It is a systemic illness presenting most commonly with chronic, symmetric poly-arthritis. It commonly presents with swelling, pain, morning stiffness which can progress to disuse osteoporosis and muscle wasting, joint destruction and functional impairment [9, 10]. In India too, the incidence of RA is increasing. The aetiology of RA is still unknown, and seems to be multi-factorial. Chronic inflammation is known to play

**Correspondence*
Dr. Atul Rajpara
Assistant Professor, Department of Pharmacology, American International Institute of Medical science, Udaipur, Rajasthan, India.
E-mail: atulrajpara@gmail.com

a role which leads to various local and systemic manifestations and production of rheumatoid factor [11]. There is no curative treatment for RA [12]. Optimal treatment includes combination of patient's education, counselling, physical and occupational therapy, pharmacotherapy, and at last surgery with pharmacotherapy being the mainstay of treatment. However, various drugs used for treatment of RA produce an array of adverse reactions on long term use [13]. Various experimental and clinical studies have shown that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) modulate pro-inflammatory mediators. Increased dietary intake of ω-3 PUFAs or direct preformed fish derived EPA, DHA plays an important role in countering inflammation via alteration of the production of anti-inflammatory anti-proliferative eicosanoids and cytokines [14-16]. Flaxseed oil is derived from seeds of plant Linium usitatissimum, a rich source of omega-3 PUFAs which provides linoleic acid (LA) and alpha linolenic acid (ALA) in a 1:4 ratio [17-19]. ALA is a precursor of EPA and DHA (Long chain omega-3 PUFAs) [20]. Hence, the present study was planned to evaluate the therapeutic efficacy, tolerability and safety of flaxseed oil (ω-3 EFAs) supplementation along with current treatment regimens for improvement of clinical inflammatory symptoms in the rheumatoid arthritis (RA). As per our knowledge, no such study using this flaxseed oil (nutraceutical ω-3FA) has been conducted in the patients suffering from RA in the state of Gujarat, India, so present study should help in generating fresh evidences in this locality.

Materials and Methods

This was an interventional, prospective, single blinded study conducted at the outpatient orthopaedic department of a tertiary care teaching hospital and a private orthopaedic hospital in a city of western Gujarat, India. Prior permission to conduct the study was obtained from the medical superintendent of the hospital. Patients of either sex, of 25-50 years, who were diagnosed to be suffering from rheumatoid arthritis (RA) according to the American College of Rheumatology criteria were included in the study after obtaining their written informed consent. Patients with known food allergies, and/or those who had any other Musculo-skeletal disease, those suffering from concomitant chronic disease 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 the clinicians were unable to comply with the study protocol, were excluded. All subject received first line therapy i.e. NSAIDs for the control of their symptoms. A total of 70 patients were finally enrolled in the study according to selection criteria. Patients were randomized and equally distributed into two groups i.e. placebo and test group, with 35 patients in each group. At baseline, details of clinical examination were recorded.The parameters were assessed to evaluate therapeutic efficacy and tolerability of placebo and flaxseed oil in both groups at 0-day [18] are Pain at rest, Pain on movement, swelling of affected joint(s), Tenderness of joint, Duration of morning stiffness and Ability to perform physical activities. Pain, swelling, tenderness and ability for work performance were assessed on a '4 point' categorical scale while duration of morning stiffness 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 also measured on a 4-point scale where 0 = none, 1 = palpable, 2 = palpable and visible, 3 = distortion of joint centres. Tenderness was measured on a 4-point categorical scale, with Grade 0 = No pain on pressure, Grade 1 = Slight pain on pressure, Grade 2 =Pain and winching, Grade 3 = Patient did not allow palpation 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 = No activity is possible. Score was derived by the investigator's assessment and by the patient's response to the investigator in response to symptoms. Observer's opinion for degree of disease symptoms was recorded on the basis of pain score given by H.F.H. Hill [21] in below Table- 1A and therapeutic efficacy was rated on the basis of results and patient's experience at the end of the study period as given in below Table- 1 B:

Table 1 A: Pain score

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

Table 1B: Basis of results and patient's experience

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

Placebo group was prescribed liquid paraffin in soft gelatine capsule in a dose of 2 capsules (1 ml/capsule) TDS for a period of 6 weeks. Test group received flaxseed oil in soft gelatine capsule in a dose of 2 capsules (150 ml/capsule) TDS for a period of 6 weeks. Above mentioned parameters and laboratory investigations were recorded on day 0 (base line) and at the end of 6 week of treatment.

Patients and attendants were instructed to report any untoward occurrence immediately to investigators and aggravation of the clinical symptoms, if present.

Statistical Analysis

Demographic characteristics, height and body weight of both groups were analysed for statistically significant difference using unpaired t-test. Therapeutic efficacy of placebo and flaxseed oil treatment on improvement of inflammatory symptoms as well as its safety and tolerability (effect on LFT, RFT, BT, CT, PT, haemoglobin, total count and FBS) were analysed for statistically significant difference using paired t-test (intra-group comparison) and unpaired t-test (inter-group comparison).

Result

A total of 70 patients, who matched the selection criteria and gave written informed consent were included in the present study. These patients were distributed equally (n=35) in either placebo/ flaxseed oil group. All patients completed study protocol successfully without any drop out. Common complaints by enrolled patients' joint pain at rest and on movement, joint swelling and morning stiffness were similar in both groups at base line (Table 2).

Table 2: Common complains at base line

Complaints	Placebo-group (n=35)		Test (flaxseed oil) group (n=35)	
	No. of patient	%	No. of patient	%
Joint pain	35	100	35	100
Joint-swelling	35	100	35	100
Morning-stiffness	35	100	35	100

At the end of the 6-weeks of treatment, a significant lowering in the score values (mean ± SD) of different parameters physical performance as compare to base line values was observed, while no significant change was observed in the placebo group with regards to the same (Tables 3 and 4). Where, the observed baseline scores for all these parameters were similar in both the groups. As compared to placebo it has been observed that EFA therapy lead to greater and statistically significant ($p< 0.001$) changes (decrease in mean score, i.e. improvement) in all the parameters

Table 3: Different parameters at the end of six weeks compared to base line

Complaints (Parameter)	Mean pain score at rest		Mean pain score on movement		Mean score of joint swelling		Mean score of tenderness	
	Placebo	Test	Placebo	Test	Placebo	Test	Placebo	Test
Base-line (0-day)	1.94 ± 0.42	1.97 ± 0.45	2± 0.34	1.94 ±0.42	1.69 ± 0.47	1.71 ± 0.57	1.74 ± 0.50	1.74 ± 0.50
At the end of 6th week	1.94 ± 0.36	0.93 ± 0.45	2.1± 0.40	0.9 ± 0.5	1.87 ± 0.43	0.73 ± 0.58	1.84 ± 0.52	0.73 ± 0.45
Difference: base-line to end of 6th week	0.03 ± 0.31 (NS)	1.07*** ± 0.25	-0.1±0.25 (NS)	1.1*** ±0.4	-0.13 ± 0.34 (NS)	1.03*** ± 0.41	-0.1 ± 0.30 (NS)	1.1*** ± 0.31

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

Table 4: Clinical symptoms at base line and at the end of 6 week

Clinical Symptoms (Parameter)	Mean duration of morning stiffness (in minutes)		Mean score for ability to perform physical activities	
	Placebo	Test	Placebo	Test
Base-line (0-day)	24.1± 4.11	24.4±5.11	1.74 ± 0.51	1.77±0.49
At the end of 6th week	25.2± 3.20	19.5± 4.71	1.81 ± 0.60	0.67 ± 3.18
Difference: base-line to end of 6th week	0.5±3.26 (NS)	5.03***±1.92	0.1±0.25(NS)	1.13***±0.35

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

In addition to clinical parameters, a significant reduction in ESR in the test drug treated group was observed as compared to placebo treated group at the end of six weeks, values are shown in table-5.

Table 5: Changes in ESR value at base line and at the end of six weeks

	ESR (mm/hour)		ESR (mm/hour)	
	Placebo group		Test (EFAS)group	
Parameter	Mean	SD	Mean	SD
Baseline ‘b’	33.1	± 5.83	34.8	± 6.18
End of 6 weeks ‘e’	33.5	± 5.76	29	± 5.3
Difference ‘b’ to ‘e’	0.4	± 1.35	5.58	1.74
	NS	NS	***	***

NS = Non-Significant; *** = Highly Significant

It has been observed that greater number of patients in the EFAs treated group showed an improvement in symptoms as compared to placebo treatment (Table 6).

Table 6: Clinical symptoms (noted by observer) at baseline and at the end of six weeks

	Placebo-group No. of patients responded (n=31)				Test group No. of patients responded (n=30)			
	Base line(n = 31)		At the end of six weeks(n = 31)		Base line (n = 30)		At the end of six weeks(n = 30)	
	No of Patient	%	No of Patient	%	No of Patient	%	No of Patient	%
Nil or Remitted	-	-	-	-	-	-	4	13
Mild	3	10	3	10	3	10	24	80
Moderate	26	84	27	87	24	80	2	7
Severe	2	6	1	3	3	10	-	-
Total	31	100	31	100	30	100	30	100

Discussion

The present study was conducted at a tertiary care teaching hospital and at a private multispecialty hospital in the state of Gujarat, India, to study efficacy, tolerability and safety of flaxseed oil supplementary treatment in newly diagnosed rheumatoid arthritis (RA) patients. Flaxseed oil is a rich source of alfa linoleanic acid (α-LA) which is a good precursor of omega-3-PUFA i.e. EPA and DHA [19,20]. In this present study, a total of 70 patients of either sex, between the age group of 25-50 years who were newly diagnosed to be suffering from RA were enrolled after taking their willingly written informed consent. In our study the observed ratio of male and female participants in placebo group was 1:1.6 and in test groups was 1:1.4 which as well as the common complains i.e. joint pain, joint swelling and morning stiffness were reported by all participants at enrolment, which are cardinal features of rheumatoid arthritis (RA) was similar to that of the observation studied by Adami S [22]. At the end of 6 weeks of treatment, a significant reduction in mean scores values of pain at rest and movement, joint swelling and tenderness as compared to those values at baseline was observed in test group (flaxseed oil treated group) suggestive of an improvement in the cardinal symptoms of RA. However, in the placebo group, there did not observed any significant reduction in mean score values, showed that placebo treatment did not have a significant improvement in the symptoms i.e. relief of the cardinal symptoms of RA. The benefit observed in flaxseed oil group may be attributed to attenuation of inflammation due to generation of anti-inflammatory and anti-proliferative eicosanoids and cytokines by flaxseed oil (ω-3 EFA). This can reduce the symptoms and result in improvement of the above-mentioned scores.

Similarly, a reduction in the mean scores of duration of morning stiffness and ability to perform physical activities, observed in flaxseed oil treatment group, may be attributed to anti-inflammatory effect of flaxseed oil (ω-3 EFA). Similar findings were reported in studies by Van der TH et al. [23] and Robert B Zurier et al. [24,25].In the present study, a greater symptomatic improvement was also reported by patients in the test group (flaxseed oil treatment group) at the end of six weeks of treatment, which reflects the clinical benefit observed. In the present study, flaxseed oil administration was not found to affect BT, CT and PT liver function test (LFT) and renal function test (RFT) after a treatment period of six weeks. Similarly, at the end of six weeks of treatment, it was not found to affect the values of haemoglobin level, WBC count and FBS in both the groups, while, in our study, a significant reduction in ESR values was noted in the test drug treated group compared to placebo treated group, which need to be confirmed by conducting few more studies. In accordance with the biochemical effects, the beneficial anti-inflammatory effects of

dietary fish oils (which is a direct source of EPA and DHA an omega-3 PUEFAs) have been demonstrated in randomized, double-blind, placebo-controlled trials in rheumatoid arthritis (RA) [26 -28] is similar to and supports the present study. The present study was one of the first studies to evaluate vegetarian source of omega-3 EFAs (ω-3 EFA) on RA patients in the western region of Gujarat, India. Further, multicentre--longer duration clinical studies / trials is recommended to evaluate the efficacy and safety of flaxseed oil supplementation in a larger population of RA patients, and to evaluate the NSAIDs and steroid sparing potential of flaxseed oil supplementation.

Conclusion

Flaxseed oil supplementation has beneficial effects on inflammatory symptoms of RA, without any major adverse effects. Further long-term studies are recommended to evaluate the role of flaxseed oil supplementation in RA patients.

Acknowledgement

We are thankful to Medical Superintendent of civil hospital, B.J. Medical College, Ahmedabad, Gujarat (India) and scientific research committee for support during the study.

References

1. Connor W E. Importance of n-3 fatty acids in health and disease. Am. J.Clin. Nutri., 2000;71(Supplement):171-175.
2. Das UN. Biological significance of essential fatty acids. J Assoc Physicians India. 2006; 54:309–319.
3. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. Nat Rev Immunol. 2015; 15:511–523.
4. Simopoulos AP. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. World Rev Nutr Diet. 2003; 92:1–22.
5. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: Nutrition or pharmacology? Br J Clin Pharmacol. 2013; 75: 645–662.
6. Serhan CN, Chiang N & Van Dyke TE. Resolving inflammation: dual anti- inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008; 8:349–361.
7. James MJ, Gibson RA & Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr. 2000;71: Suppl.; 343S–348S.
8. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. Nat Rev Immunol. 2015; 15:511–523.
9. Akbar, Umair BS; Yang, Melissa BS; Kurian, Divya BS; Mohan, Chandra-MD. A Critical Review, Omega-3 fatty acids in rheumatic diseases. Journal of Clinical Rheumatology. 2017; 23(6): 330–339.
10. Proudman SM, Cleland LG & James MJ. Dietary omega-3 fats for treatment of inflammatory joint disease: efficacy and utility. Rheum Dis Clin North Am: 2008; 34:469–479.
11. James MJ, Proudman SM & Cleland LG. Fish oil and rheumatoid arthritis: past, present and future. Proc Nutr Soc: 2010; 69:316–323.
12. Thompson PW, Tee L, McBride J, et al. Long-term NSAID use in primary care: changes over a decade and NICE risk factors for gastrointestinal adverse events. Rheumatology (Oxford) 2005; 44:1308–1310
13. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr. 2000; 71:343S–348S.
14. Calder PC. Mechanisms of action of (n-3) fatty acids. J Nutr. 2012; 142:592S–599S.
15. The omega-3 fatty acid nutritional landscape: Health benefits and sources. The journal of nutrition. 2012 ; 8:142(3):587S-91S.
16. Covington MB, Omega-3 fatty acids. Am Fam Physcian, 2004;70:133-140.
17. Health benefits of plant-derived alpha – linolaenic acid. The American Journal of Clinical Nutrition. 2014; 4:100 (supl-1):443S-448S.
18. Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence. Karger Publishers; Basel, Switzerland:2004;92:1–22
19. Jairam S, Shetty N, Krishnamurty V, Sharma VD et.al., Clinical study of the efficacy and tolerability of Diacerin in the treatment of "Mild to Moderate" osteoarthritis; A randomozed multicentred Comparative Study. The Indian Practitioner, 2005; 58 (11): 683-691.
20. Adami S,Braga V, Zamboni M, Gatti D, Rossini M, Bakri J, Battaglia E. et al study-5. Relationship between lipid and bone mass in 2 cohorts of healthy women and men. Calcified tissue international. 2004; 1:74(2):136-42
21. Van der TH, Tulleken JE, Limburg PC et al. Effect of Omega 3 fatty acid supplementation in

Rheumatoid arthritis. Ann Rheum Dis 1990 ; 49 (2): 76-80.
22. Zurier RB, Rossetti RG, Demerco Dm, Liu NY. Gamma-Linoleic acid treatment of Rheumatoid arthritis – A Randomozed Placebo Controlled Trial. Arthritis and Rheumatism. 1996; 39(11): 1808 -1817.
23. Park Y, Lee A, Shim SC, et al. Effect of n-3 polyunsaturated fatty acid supplementation in patients with rheumatoid arthritis: a 16-week randomized, double-blind, placebo-controlled, parallel-design multicenter study in Korea. J Nutr Biochem. 2013;24:1367–1372.
24. Lorenz R, Loeschke K. Placebo-Controlled Trials of omega -3 fatty acids in chronic inflammatory disease and effects of fatty acids and lipids in Health and disease. 1994; 76: 143 -15.
25. Adam O, Beringer C, Kless T, et al. Anti-inflammatory effects of a low arachidonic Acid diet and fish oil in patients with rheumatoid arthritis. Rheumatol Int. 2003; 23:27–36.
26. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010; 2: 355 -374.

Conflict of Interest: Nil
Source of support:Nil