**Scholars Journal of Applied Medical Sciences (SJAMS)**
***Abbreviated Key Title: Sch. J. App. Med. Sci.***
**ISSN 2320-6691 (Online)**
**ISSN 2347-954X (Print)**

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Pharmacology

# An Evaluation of Effect of Flaxseed Oil (N-3 Fatty Acid) Treatment on Lipid Parameters and Its Tolerability in Dyslipidemic Patients

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**Original Research Article**

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**Article History**
*Received: 16.01.2018*
*Accepted: 22.01.2018*
*Published: 30.01.2018*

**DOI:**
10.36347/sjams.2018.v06i01.047

**Abstract:** To evaluate the effect of flaxseed oil treatment on lipid parameters and to assess tolerability of the same in dyslipidemic patients. An interventional, prospective study was conducted on outpatients of either gender in the age group of 18-60 years. A total of 120 patients, newly diagnosed to be suffering from dyslipidemia, were enrolled in the study. Patients were randomly divided into two groups, namely placebo group and test group with 60 patients in each group. Both groups were advised dietary fat restriction for one month (Phase I), followed by administration of 2-soft gelatin capsule-BD of liquid paraffin (1 ml) in placebo group and 2-soft gelatin capsule-BD of flaxseed oil (150 mg) in test group for a period of six weeks along with dietary restriction phase-II. Lipid profile, Fasting blood sugar (FBS), Bleeding time (BT), Clotting time (CT), Prothrombin time (PT), Renal function test (RFT) and liver function tests (LFT) were recorded at base line, at the end of Phase I (dietary restriction) and Phase II (placebo and test drug treatment). A significant lowering of total cholesterol (TC), LDL, TG and VLDL and an increase in HDL values as compared to baseline was observed in both groups after phase I. At the end of phase II treatment, further improvement in these parameters was observed in test group (flaxseed oil treatment) but not in the placebo group. No adverse impact was noted FBS, LFT, RFT, BT, CT and PT in both groups. Adverse events were comparable and resolved without a need of stoppage of drug in both groups. To conclude dietary restriction and flaxseed oil treatment reduced TC, LDL, VLDL and TG and increased HDL in patients of dyslipidemia without any adverse effect on blood parameters, liver and renal function during a 6 week study. Long term studies are recommended to evaluate the anti-dyslipidemic effects and safety of flaxseed oil in a larger population.
**Keywords:** Flaxseed oil, dyslipidemia, dietary restriction.

## INTRODUCTION

Cardiovascular disease (CVD) continues to be an important cause of death in United States, Europe and many other developed and developing countries [1]. High plasma concentrations of cholesterol, particularly of low-density-lipoprotein (LDL) and Triglyceride (TG), is one of the principal risk factors for atherosclerosis [2] and contributes to morbidity and mortality. One of the main therapeutic goals is to restore the elevated levels of plasma lipids, notably cholesterol [3].

Dietary fat plays an important role in CVD by affecting atherogenesis, thrombosis and coronary circulation. Saturated fatty acids (SAFs) increase the risk of coronary heart disease (CHD), whereas monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) reduce the risk by lowering plasma lipids [2].

n-3 fatty acids (n-3-FA) are polyunsaturated fatty acids (PUFA), obtained from marine (cold water fish) and vegetable (walnuts, soy, flaxseed etc.) sources. n-3 Fatty acids include Eicosapantaenoic acid (EPA), Docosahexaenoic acid (DHA) and α-linoleanic acid (ALA). These lower serum cholesterol, LDL, VLDL and TG. In addition, these provide anti-inflammatory and anti-proliferative eicosanoids and cytokines, which halt the progression of atherosclerosis [4]. Several studies have demonstrated the cardioprotective effect of EPA and ALA [5-7].

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 effect on lipid parameters has not been studied adequately in Indian population. The present study aimed to assess effect and tolerability of Flaxseed-oil (FO) in dyslipidemic patients at a tertiary care hospital and a private clinic in Gujarat, India.

## MATERIALS AND METHODS

This was an interventional, prospective study conducted at the outpatient Medicine department of a tertiary care teaching hospital and a private clinic in a city of Guajart. Permission to conduct the study was obtained from Medical superintendent of the hospital. The study was conducted over a period of 2 years i.e. December 2005 to November 2007.

Patients of either gender in the age group of 18-60 years, who were detected to have an abnormal lipid profile on investigation and not receiving any medication for dyslipidaemia, were included in the study after obtaining written informed consent. Patients with known food allergies, past or present smoking habit, history of chronic disease like hypertension or other cardiovascular disease, diabetes mellitus those with any other abnormal laboratory parameters, pregnant and lactating females and those who, according to clinician were unable to comply with the study protocol, were excluded.

A total of 120 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 60 patients. Following enrolment, patients of both groups were instructed to restrict the fat consumption to 30% of their routine intake (Phase I; dietary restriction) for a period of 30 days. Following this, placebo group was prescribed liquid paraffin in soft gelatine capsule (1 ml/capsule); 2 capsules BD for a period of 6 weeks in addition to dietary restriction. Similarly, test group received flaxseed oil in soft gelatine capsule (150 mg/capsule); 2 capsules BD for a period of 6 weeks in addition to dietary restriction (Phase II treatment).

### Investigations

At enrolment (baseline); reports of following investigations in patients of both groups were recorded: (1) Lipid profile (2) Fasting blood sugar (FBS) (3) Bleeding time (BT) (4) Clotting time [CT] (5) Prothrombin time [PT] (6) Renal function test [RFT] (7) Liver function test [LFT] and (8) Blood pressure recording (BP). Same investigations were recorded at the end of Phase I (dietary restriction) and Phase II (placebo or test drug treatment).

## STATISTICAL ANALYSIS

Demographic characteristics, height and body weight of patients of both groups were analysed for statistically significant difference using unpaired t- test. Effects of dietary restriction on lipid parameters and effect of placebo and flaxseed oil treatment on lipid parameters, LFT, RFT, BT, CT, PT, Haemoglobin, total count and FBS were analysed for statistical significance using paired t test (intragroup comparison) and unpaired t test (intergroup comparison).

## RESULTS

A total of 120 patients were enrolled in the study according to the selection criteria as mentioned previously. Of these, 60 patients received placebo treatment (liquid paraffin in soft gelatine capsule) and 60 patients were prescribed flaxseed oil (test group) (soft gelatine capsule). Baseline characteristics of these groups are shown in table 1. Both the groups were similar with regards to baseline characteristics.

**Table-1: Baseline characteristics of patients enrolled in placebo group (n=60) and test group (n=60)**

| Baseline Characteristics | Placebo group Average values | Test group Average values |
|---|---|---|
| Age ( mean ± SD) years | 42.7 ± 5.5 | 43.95 ± 5.6 |
| Males<br>Females | 31<br>29 | 33<br>27 |
| Height (in meters)<br>Weight (in Kg) | 1.58<br>62.2 | 1.56<br>61 |
| Total cholesterol | 219 | 218 |
| HDL mg/dl | 37 | 37 |
| LDL mg/dl | 138 | 137 |
| TG mg/dl | 215 | 219 |
| VLDL mg/dl | 43 | 44 |
| FBS mg% | 81.03 | 82.17 |
| Blood pressure (systolic/diastolic) | 122 /80mm Hg | 123/80mmHg |

A significant lowering of total cholesterol (TC), LDL, TG and VLDL and an increase in HDL values as compared to baseline values was observed in patients of both groups after one month of dietary restriction (Phase I) (Table 2 and table 3). Five patients in the placebo group and three patients in test group were lost to follow up after phase I and were not included in further analysis. In the placebo group, phase II treatment (placebo+ dietary restriction) did not further improve these parameters at the end of six weeks following phase I (Table 2). In test group, phase II treatment (flaxseed oil+ dietary restriction) resulted in significant lowering of TC, LDL, TG and VLDL and a significant increase in HDL level as compared to that at the end of phase I treatment (Table 3).

**Table-2: Effect of dietary restriction (phase I) (n=60) and dietary restriction+ placebo (Phase II treatment) (n=55) on lipid parameters in dyslipidaemic patients**

| Lipid parameters (mg/dL) | Base-line (n=60) | At end of phase I (n=60) | At end of phase II (n=55) |
|---|---|---|---|
| Total-cholesterol | 219.9 ± 18.52 | 206.5 ± 17.5*** | 208.3 ± 17 |
| HDL | 39.4 ± 5.14 | 37.0 ± 4.79*** | 37.1 ± 4.8 |
| LDL | 137.3 ± 17.35 | 129.2 ± 16.59*** | 130.9 ± 16.42 |
| Triglyceride (TG) | 216 ± 19.28 | 201.3 ± 19.06*** | 202 ± 17.97 |
| VLDL | 43.2 ± 3.86 | 40.3 ± 3.81*** | 40.4 ± 3.59 |
| Total-CH:HDL | 5.66 ± 0.75 | 5.64 ± 0.74 | 5.7 ± 0.76 |
| LDL:HDL | 3.55 ± 0.68 | 3.55 ± 0.68 | 3.59 ± 0.69 |

Values are expressed as mean ± SD

***P < 0.001 as compared to respective parameter at baseline

No significant difference was observed between parameters at the end of phase I and those at the end of phase II

**Table-3: Effect of dietary restriction (phase I treatment) (n=60) and dietary restriction+ flaxseed oil (Phase II treatment) (n=57) on lipid parameters in patients**

| Lipid parameters (mg/dl) | Base-line (n=60) | At end of phase I (n=60) | At the end of phase II treatment (n=57) |
|---|---|---|---|
| Total-cholesterol | 217.1 ± 15.53 | 204.1 ± 15.50*** | 187.3 ± 13.98# |
| HDL | 37.1 ± 6.1 | 36.7 ± 5.35** | 41.3 ± 5.27# |
| LDL | 135.4 ± 15.49 | 126.8 ± 15.85*** | 113.4 ± 15.21# |
| Triglyceride (TG) | 219.1 ±18.7 | 202.9 ± 17.95*** | 162.8 ± 17.17# |
| VLDL | 43.8 ± 3.74 | 40.6 ± 3.59*** | 32.6 ± 3.43# |
| Total-CH:HDL | 5.87 ± 1.02 | 5.67 ± 0.9*** | 4.61 ± 0.69# |
| LDL:HDL | 3.68 ± 0.83 | 3.54 ± 0.76*** | 3.13 ± 0.64# |

Values are expressed as mean ± SD

***P < 0.001 as compared to respective parameter at baseline; ** P< 0.01 as compared to respective parameter at baseline

# P < 0.001 as compared to respective parameter at the end of phase I

Comparison between placebo treatment and flaxseed oil treatment on lipid parameters showed that flaxseed oil significantly reduced TC, LDL, VLDL and TG and significantly improved HDL values at the end of six weeks treatment as compared to placebo (Table 4).

**Table-4: Comparison of changes in lipid parameters from phase I (Mean ± SD) with placebo treatment and flaxseed oil treatment at the end of six weeks**

| Lipid parameters (mg/dL) | Change in lipid parameters in placebo group from phase I | Change in lipid parameter with flaxseed oil treatment from phase I |
|---|---|---|
| Total-Cholesterol | -1.87 ± 3.76 | 16.7 ± 5.23*** |
| HDL | -0.0 ±1.2 | -4.6 ± 2.4*** |
| LDL | -1.7 ± 3.9 | 3.01 ± 6.21*** |
| TG | -0.76 ± 3.11 | 40.1 ± 10.8*** |
| VLDL | -0.15 ± 0.62 | 8.01 ± 2.16*** |
| To. CH.:HDL | -0.1 ± 0.24 | 1.06 ± 0.42*** |
| LDL:HDL | -0.0 ± 0.21 | 0.41 ± 0.25*** |

*** P< 0.001 as compared to placebo group in respective parameter

Negative value indicates an increase in lipid & lipoprotein levels

**Safety assessment**

A total of 64 adverse events were observed in placebo group and 41 were observed in flaxseed oil treatment group (table 5). Most adverse events were mild, self-limiting and did not warrant withdrawal of treatment.

**Table-5: Adverse events observed with placebo(n=55) and flaxseed oil(n=57) treatment**

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

**Laboratory parameters**

Bleeding time, clotting time, prothrombin time, hemoglobin, total count and fasting blood sugar, AST, ALT, s. bilirubin, s. urea, s. creatinine values at baseline and at the end of follow up period were compared. No statistically significant difference was observed in these parameters between the baseline values and those at the end of phase II in both placebo and flaxseed oil treatment groups (table 6a and 6b).

**Table-6a: Values (Mean ± SD) of bleeding time, clotting time, prothrombin time, Haemoglobin, total WBC count and fasting blood sugar in patients at base-line and at end of phase II treatment**

| | BT (in min.) | | CT (in min.) | | PT (in sec.) | | Haemoglobin (g/dL) | | Total Count (cells/mm3) | | FBS (mg/dL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 ± 0.9 | 11.0 ± 1.2 | 7923 ± 697 | 7935 ± 681.2 | 91.0 ± 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 ± 0.7 | 11.3 ± 0.8 | 8048 ± 789.5 | 7979 ± 697.4 | 94.7 ± 5.7 | 95.4 ± 5.03 |

BT: Bleeding time; CT: clotting time; PT: prothrombin time (control value for PT=14 sec) FBS: Fasting blood sugar
No significant difference was observed in respective parameters in both groups at the end of six weeks as compared to baseline values

**Table-6b: Values (Mean ± SD) of liver function test and renal function test in patients at baseline and at the end of phase II 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 grouo | Placebo group | Test grouo |
| | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD | Mean ±SD |
| At 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 respective phase II treatment | 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 |

No significant difference was observed in respective parameters in both groups at the end of phase II as compared to baseline values

## DISCUSSION

The present study was conducted at a tertiary care hospital and a private clinic in Gujarat, India to study the effect and safety of flaxseed oil treatment in dyslipidaemic patients. The study was conducted over a period of 2 years and involved 60 patients each in placebo and flaxseed oil treatment groups. Few patients in both groups were lost to follow up at the end of phase I (dietary restriction) and were excluded from further analysis.

Dietary restriction, in the form of 30% reduction in routine fat intake, was advised for both groups for a period of one month. Dietary restriction resulted in improvement of lipid parameters in study population. Such measures are routinely employed in dyslipidemic patients as a non-pharmacological measure to improve the lipid profile and usually serve as adjunct to drug therapy.

Subsequently, patients received either placebo (liquid paraffin 1 ml soft gelatin capsule, 2 capsules BD) or flaxseed oil (150 mg soft gelatin capsule, 2 capsules BD) for a period of 6 weeks in addition to dietary restriction. As expected, placebo treatment did not alter lipid parameters significantly in comparison to that at the end of phase I dietary restriction. However, flaxseed oil treatment significantly improved the lipoprotein levels in treatment group. The effect was evident in the form of reduction in TC, LDL, VLDL and TG and improvement in HDL levels. Further, a reduction in Total CH: HDL and LDL: HDL ratio suggested a beneficial effect of flaxseed oil on lipid profile which if sustained can be cardio-protective. Also, flaxseed oil treatment was superior to placebo in terms of improvement of lipid parameters. Reduction in TC, LDL, VLDL and TG are known to reduce the CV risk [2, 5, 6, 7, 4, 8] Reduction in lipid parameters with flaxseed oil treatment has been observed in various animal studies [9,13]. Kawakami Y et al. reported that flaxseed oil treatment significantly reduced sd-LDL levels in subjects with TG > 100 mg/dl [10]. Another study demonstrated reduction in TG levels with flaxseed oil treatment in hyperlipidaemia patients [11]. However, Prasad et al. in a review suggested that flaxseed oil does not significantly affect lipid parameters except for a slight reduction in TG levels [12]. Further large scale studies are required to determine the long term effect of flaxseed oil treatment on lipid profile in patients of dyslipidaemia and to identify possible mechanisms of action.

Safety assessment in the present study was conducted using assessment of adverse events and effect of 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, however, stoppage of drug therapy was not required 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. However, a longer duration study is recommended to evaluate these parameters in view of chronic therapy and to establish the safety profile of flaxseed oil.

## CONCLUSION

Dietary restriction and flaxseed oil treatment reduced TC, LDL, VLDL and TG and increased HDL in patients of dyslipidemia without any adverse effect on blood parameters, liver and renal function during a 6 week study. Further long term studies are recommended to evaluate the anti-dyslipidemic effects and safety of flaxseed oil in a larger population.

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