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Research Article

Efficacy and safety of a combination therapy of atorvastatin and krill oil versus atorvastatin and niacin in dyslipidemia: a randomized, open, and comparator study

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ABSTRACT

Background: Atherosclerotic cardiovascular disease is a major health problem, with CAD being the leading cause of mortality. Epidemiologic data strongly associate high CAD risk to elevated total and LDL cholesterol and low levels of HDL cholesterol. Combination therapy is often required to achieve multiple lipid treatment goals, and ≥50% reduction in low-density lipoprotein. Niacin/statin combination therapy may promote the cost-effective achievement of OLVs in several at-risk patient populations. Krill oil is extracted from Antarctic krill, *Euphausia superba*, a zooplankton crustacean rich in phospholipids. Krill oil significantly reduces total cholesterol, LDL, and triglycerides, and increase HDL levels and has been found to be effective in the management of hyperlipidemia and long-term regulation of blood lipids. The aim of this study is to compare the Efficacy and Safety of a combination therapy of statin and krill oil versus Statin and Niacin in dyslipidemia.
Methods: 30 eligible patients were randomized in a 12 week, open-label, comparative (2-arm, 1:1), prospective study into 2 arms, the first receiving atorvastatin 10mg od and krill oil 500mg bid and the second receiving atorvastatin 10mg od and niacin 375mg od. The primary endpoint of the study was a comparative assessment of change in lipid profile (LDL, TG, HDL) from baseline and after 12 weeks. The secondary endpoint involved recording all the adverse effects during the study.
Results: Analysis of the baseline and post 12 week lipid levels by non-parametric unpaired 't' test (Mann-Whitney test) showed a statistically significant change in two of the lipid levels (i.e. LDL – p=0.0037 in favour of statin and niacin and HDL – p=0.0003 in favour of statin and niacin). However the triglyceride levels showed no significant change in the two groups (p=0.2452).
Conclusions: In our study the conventional combination therapy of statin and niacin is found to be more efficacious than the newer statin and krill oil combination in lowering LDL levels and increasing HDL levels in dyslipidemic patients. A further study with a higher sample size could confirm the findings of this study.

Keywords: Krill oil, Dyslipidemia, Atherosclerosis

INTRODUCTION

Lipid lowering drugs have been used in well-controlled randomized studies of patients with high cholesterol levels caused primarily by elevated levels of low density lipoproteins (LDL).[1] Several other studies have demonstrated that intensive lowering of serum total cholesterol or LDL cholesterol may retard progression of coronary atherosclerosis.[2-4]

Epidemiologic studies have shown that, in addition to elevated LDL cholesterol levels, low levels of high-density lipoprotein (HDL) cholesterol are an independent predictor of the risk of coronary heart disease, with a strong inverse association between HDL cholesterol

levels and the rates of incident coronary heart disease events. New approaches to lipid lowering include new uses of proven treatments and development of novel agents. Several large-scale clinical trials are assessing whether additional reduction of low-density lipoprotein cholesterol (LDL-C) levels with statin therapy results in additional benefit in coronary artery disease prevention. Combination approaches hold considerable promise, including combined use of statins with fibrates, niacin, and the new sterol absorption inhibitors.[5] Among currently available statins, atorvastatin produces greatest reduction in LDL-C levels over its dose range of 10 to 80 mg.[6]

Studies have consistently shown that the higher the plasma level of high-density lipoprotein cholesterol (HDL-C), the lower the risk of cardiovascular events, suggesting that raising HDL-C may be beneficial.[7] Studies in animals with atherosclerosis show that raising HDL-C via genetic modification of the animal or direct infusion of the molecule has a favorable impact on both the size and the structure of experimental plaque.[8,9]

In addition to raising HDL-C levels more effectively than any other agent available today, niacin also lowers the levels of LDL-C, triglycerides, and lipoprotein (a).[10] Before statins were available, the Coronary Drug Project found that niacin reduced the rate of nonfatal myocardial infarction and the 15-year mortality rate.[11] In addition, niacin has been shown to slow the progression of carotid intimal-medial thickness and coronary atherosclerosis, and even to reverse these processes in some trials.[12,13]

Niacin is the most effective agent for raising HDL-C levels, and pharmacoeconomic modeling suggests that niacin/statin combination therapy may promote the cost-effective achievement of in several at-risk patient populations.[14,15] The combination of statin and niacin was very well tolerated in one of the studies.[16-18]

Antarctic krill are ancestors of clay fish and prawn. They have a slow evolutionary speed, and are not good at swimming. They are distributed in Vancouver Saigan sea area, Russia, Ukraine and so on. They have the largest amount of protein among all organisms so far, over 16% in wet weight while over 65% in dry weight. Antarctic krill oil (KO) contain more than 30% of essential eicosapentaenoic acid (EPA, C:20:5, n-3) and docosahexaenoic acid (DHA, C:22:6, n-3) as well as astaxanthin (provitamin E) in concentrations of 200 – 400 ppm.[19] Besides, they also have abundant phospholipids, flavonoids, vitamin A, alphalinolenic acid (ALA), astacin and other nutrients.[20]

Krill oil has hypolipidemic properties and has shown to reduce the body weight and serum triglycerides, total cholesterol and LDL-C levels significantly. Also, it increases HDL levels. Thus, the consumption of KO may provide benefit to control serum lipid levels in certain diseases.[21,22] Hence we hypothesize that KO could be a good add-on drug to the gold standard statins. The aim of this study was to compare efficacy and safety of a combination therapy of statin and krill oil versus statin and niacin in dyslipidemia in adult Indian dyslipidemia patients.

METHODS

Trial design

This was a randomized, open-label, comparative (2-arm), prospective 12 week study. Treatment consisted of 2 arms: 1st arm – atorvastatin 10mg once daily and krill oil 500mg twice daily orally and 2nd arm – atorvastatin 10mg once daily and niacin 375mg once daily orally. Patents who met lipid criteria were randomized after or within 1 week of screening to one of the two treatments in a 1:1 ratio. The study was approved by the institutional ethics committee (IEC) and all included patients gave their written informed consent prior to entry into the study and the study was performed in accordance with the ethical principles consistent with good clinical practice and ICH guidelines. Patients were evaluated after 6 weeks for drug compliance and adverse effects and after 12 weeks for repeat FLP levels and adverse effects.

Endpoints

Primary endpoint of the study was comparative assessment of change in LDL-C, triglyceride, and HDL-C concentrations from baseline to 12 weeks in both the groups. Secondary endpoints included safety assessment by doing routine hematological and biochemical investigations. Patients were also observed for any adverse signs and symptoms during and for 4 weeks after the study.

Inclusion criteria

Men and non-pregnant women with uncomplicated dyslipidemia between 18 to 80 years having LDL-C levels between 160 and 250 mg/dl, triglyceride concentrations of < 400mg/dl, HDL-C concentrations < 40 mg/dl (in males) and < 50mg/dl (in females).

Exclusion criteria

Included history of coronary artery disease; congestive cardiac failure; chronic kidney disease; ischemic heart disease; myocardial infarction; malignancy; serious or unstable medical or psychological conditions that could compromise the patient's safety or successful study participation; chronic hepatic disease; pregnancy and lactation; history of smoking, drug or alcohol abuse; use of concomitant medications known to affect the lipid profile or present a potential safety concern; BMI ≤ 23; refusal to give written informed consent voluntarily and any other medical condition that, in the opinion of the investigator, may be an unacceptable additional risk to the patient.

Safety assessments included recording of treatment-emergent adverse events (adverse events that started or worsened during randomized treatment), hematological and biochemical measurements, and physical examination.

The change in the lipid parameters from baseline to the end of the study was analyzed using the Student's t test in GPIS version 3 software.

Patient characteristics

A total of 50 patients (25 in each arm) were included in the study and all the 50 patients completed the study. Mean age of the patients were 48.36 years in the niacin group and 50.23 years in the krill oil group at basal level and mean height and weight of patients were comparable in both the groups. Of the total 66% were males and 34% were females. Patients were selected very carefully as per the inclusion/exclusion criteria and the comorbid conditions were minimal/clinically not significant/well under control. Strict diet control was advised in both the groups.

RESULTS

Efficacy

Percentage changes in LDL-C, HDL-C and triglycerides from baseline to 12 weeks were the primary efficacy parameter. Analysis of the baseline and post 12 week lipid levels (LDL-C, HDL-C & triglycerides) by non-parametric unpaired 't' test (Mann-Whitney test) using GPIS software showed a statistically significant change in two of the lipid levels (i.e. LDL – p=0.0037 and HDL – p=0.0003, both in favour of statin and niacin). (Table 1 and Table 2) i.e. the drop in LDL-C and the rise in HDL-C levels were statistically significant in the niacin + statin group than the krill oil and statin group. However the triglyceride levels showed no significant change in the two groups (p=0.2452) (Table 3). The statistical tests were two tailed, with the level of significance being taken as p≤0.05.

Table 1: Comparison of LDL-C levels before and after administration of study drug in both groups.

Group	LDL-C at baseline (0 week) (Mean ± SEM)	LDL-C after treatment (12 weeks)* (Mean ± SEM)
Statin + Niacin	174.40 ± 5.258	92.80 ± 3.55
Statin + Krill oil	172.07 ± 5.051	131 ± 9.840

p=0.0037 by non-parametric unpaired 't' test (Mann-Whitney) for 'after' treatment values

Table 2: Comparison of HDL-C levels before and after administration of study drug in both groups.

Group	HDL-C at baseline (0 week) (Mean ± SEM)	HDL-C after treatment (12 weeks)* (Mean ± SEM)
Statin + Niacin	34.33 ± 0.88	41.60 ± 0.83
Statin + Krill oil	34.73 ± 1.08	31.0 ± 0.94

* p=0.0003 by non-parametric unpaired 't' test (Mann-Whitney) for 'after' treatment values between the two groups

Table 3: Comparison of triglyceride levels before and after administration of study drug in both groups.

Group	TG level at baseline (0 week) (Mean ± SEM)	TG after treatment (12 weeks)* (Mean ± SEM)*
Statin + Niacin	219.80 ± 6.62	152.80 ± 6.34
Statin + Krill oil	215.47 ± 13.89	193.13 ± 31.43

* p=0.245 by non-parametric unpaired 't' test (Mann-Whitney) for 'after' treatment values between the two groups

Safety

All the 3 drugs used in the study and especially the drug under study i.e. krill oil were very well tolerated over 12 weeks. Only five patients (from niacin group) complained of nausea, abdominal discomfort and headache of mild severity. There were no other significant changes in the laboratory parameters at the end of the treatment in both the groups.

DISCUSSION

Krill oil (KO) is a novel dietary supplement extracted from Antarctic krill (*Euphausia superba*). The beneficial effects of KO in the course of dyslipidemia and inflammation have been reported by several authors both in humans and in animals.[23-25]

In the present study krill oil at a dose of 1 g per day in divided doses as a combination add-on therapy (with the gold standard statins) over a 12 week period was found to statistically inferior (p<0.05 in favour of niacin and statin) to the existing combination of niacin and statin in lowering the LDL-C levels and raising the HDL-C levels. As per the current literature niacin is the best drug to increase HDL-C levels.[26] Niacin–statin treatment regimens gave augmented low-density lipoprotein (LDL)-cholesterol reduction along with favorable changes in high-density lipoprotein (HDL) cholesterol, lipoprotein (a), and triglycerides.[27] These findings have once again been reconfirmed in our study. However with respect to the triglyceride levels both the combinations were found to have a similar effect in our study (p>0.05). This

confirms the beneficial effect of krill oil in hyperlipidemia.[22]

Most of the present studies highlighting the beneficial properties of krill oil are when used in monotherapy and/or in comparison to fish oil. As far as we know this is the first study comparing combination therapies in dyslipidemia involving KO and also the first study which shows that KO (with statin) is inferior to the niacin (with statin) in controlling the lipid levels.

Low HDL has been a target of treatment for dyslipidemia since many years. However the medications studied so far were not satisfactorily effective and hence went out of favour by the physicians except niacin. Also they were not able to reduce the mortality and morbidity from MACE (major adverse cardiac events). Some of the medications even produced significant adverse effects that they are not in use anymore. As of today the most effective drug is niacin, but that too has some adverse effects.

Krill oil is newly introduced into the market even though they were naturally available since long and is being produced commercially. However the cost of krill oil capsules is perhaps a limiting factor in the widespread use of this drug. Having said so, it is always worthwhile doing a head to head comparative study with a molecule that has been the standard of care for low HDL patients so far. Krill oil 1g per day in divided doses was added to statin at twice daily dose, but it increases the daily cost of therapy in comparison with statin and niacin. Despite that krill oil with statin combination failed to increase the HDL levels significantly in comparison with statin and niacin combination.

CONCLUSIONS

From the present study we need to conclude that this combination is not financially effective/viable inspite of a similar/good safety profile like the statin-niacin combination. However whether this combination will provide a mortality or morbidity benefit from MACE need to be evaluated from a larger study with high risk population for a longer duration of follow up.

List of abbreviations

LDL **–** Low density lipoproteins
HDL – High density lipoproteins
LDL-C – Low density lipoprotein cholesterol
HDL-C – High density lipoprotein cholesterol
KO – Krill oil
EPA – Eicosa pentaenoic acid
OLVs **–** Optimal lipid values

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