

A Study to Assess the Effect of Dietary Supplementation with Soluble Fibre (Minolest®) on Lipid Levels in Normal Subjects with Hypercholesterolaemia

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Abstract

Hypercholesterolaemia is one of the major risk factors in the development of coronary artery disease. In recent years, many non-prescription treatments have become available for cholesterol lowering. MinolestP is a product that contains guar gum and psyllium as the principal active ingredients. We conducted a randomised, placebo-controlled, double-blind, parallel-group study to assess the efficacy of Minolest® as a lipid-lowering agent. Secondary aims included assessment of the effect on blood pressure and obesity. We also looked at the acceptability of the product and side effects associated with its ingestion. After a 4-week run-in period, 83 subjects were randomised to receive placebo or MinolestP (16.5g/day) for 3 months. Seven subjects defaulted follow up, 5 in the placebo group and 2 in the active treatment group. In addition, 9 subjects (5 on active treatment and 4 on placebo) had total cholesterol fall into the optimal range (<5.2 mmol/l) during the run-in phase and were removed from the study. At baseline in the active treatment group, total cholesterol was 6.1 (5.43 to 8.06) mmol/l, triglyceride 1.54 (0.56 to 4.19) mmol/l, HDL cholesterol 1.32 ± 0.43 mmol/l and LDL cholesterol 4.1 (3.10 to 6.27) mmol/l. In the placebo group, total cholesterol was 5.84 (5.32 to 8.38) mmol/l, triglyceride 1.47 (0.69 to 11.0) mmol/l, HDL cholesterol 1.15 (0.33 to 3.33) mmol/l and LDL cholesterol 3.87 (2.46 to 5.14) mmol/l. The differences in the baseline characteristics were not statistically significant except the LDL-cholesterol. Minolest® produced a 3.24% (SD = 7.85%, P = 0.020) decrease in total cholesterol and 5.45% decrease in LDL cholesterol (SD = 10.25%, P = 0.0034) but no significant difference in serum triglyceride, weight, body mass index or blood pressure. This was not seen in the placebo group. The percentage fall in LDL cholesterol increased to 7.16% and 7.37% in subjects who consumed at least 50% and 70% of the treatment respectively. There were few side effects. The authors conclude that this product has a small impact on the lipid profile and may be useful only in subjects with mild hypercholesterolaemia and a low risk of coronary artery disease.

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Key words: Cholesterol, Coronary artery disease risk, Diet, Fibre, Hyperlipidaemia

Introduction

Hypercholesterolaemia is one of the major risk factors in the development of coronary artery disease (CAD).^{1,2} In recent years, many non-prescription treatments have become available for cholesterol lowering. These are natural products and as such, are not subject to the rigorous testing required for new drugs, prior to their availability in the marketplace. However, in view of the cost of these treatments, it is important for physicians and members of the public to be aware of the true effect of these preparations so that we can make an informed cost benefit analysis.

Minolest® is a product that contains guar gum and psyllium as the principal active ingredients and can be taken as a drink in cold water or with other beverages. It

is marketed as a cholesterol-lowering agent. The effects of dietary fibre have been recognised for centuries. Supplementation of the diet with fibre has been shown to lower cholesterol levels. Thus far, there is no published data reporting the efficacy of this product as a cholesterol-lowering agent.

Aim

The aim of the study was to assess the efficacy of Minolest® as a cholesterol-lowering agent in normal subjects with hypercholesterolaemia when used as a dietary supplement.

Study Design

The study was designed as a double-blind placebo-

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controlled parallel-group comparison. There was a 4-week run-in period during which all subjects were put on placebo. Thereafter, subjects were randomly assigned to one of 2 groups. The active treatment group received 3 months of Minolest® while the placebo group was given a placebo lacking the active ingredients.

Subject Selection

Study subjects were selected from normal volunteers who were approached by the pharmaceutical company on behalf of the investigators. Subjects were selected on the basis of cholesterol level >5.2 mmol/l, normal blood pressure, normal fasting blood glucose (<6.0 mmol/l), no significant past medical history nor any regular medication. Subjects who had pre-existing cardiac, liver and renal diseases were specifically excluded. No subjects had major illnesses or surgery in the 3 months prior to the study.

Materials and Methods

Subjects made three visits to the specialist outpatient clinic. At visit 1 after a 10 hour fast, informed consent was obtained and venesection performed. Blood was sent for a full lipid profile [total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG)], as well as plasma glucose. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Serum for the lipid profile was collected in plain tubes. Plasma for glucose was collected in fluoride oxalate tubes. The serum TC, TG, HDL-C and plasma glucose were assayed using dry chemistry methods using the Kodak Ektachem Clinical Chemistry Slide and read on the Kodak Ektachem 700 analyser in the Biochemistry Department of the Singapore General Hospital.

All subjects were counselled on a low fat diet and exercise programme by the investigating physicians. They were then entered into a 4-week run-in period during which they were given placebo.

Subjects who returned for the second visit were randomised into active treatment or placebo groups. At this visit, the lipid profile was repeated. Subjects whose total cholesterol had fallen below 5.2 mmol/l at the second visit were withdrawn from the study by the trial coordinator. Following randomisation, subjects were given Minolest® or placebo and asked to take the preparation 3 times a day dissolved in water and before meals. Anthropometric measurements of obesity and blood pressure were taken. Blood pressure (BP) measurement was carried out after 15 minutes rest in a quiet environment. A mercury sphygmomanometer was used on the patient's left arm with the patient seated and two measurements were taken with a 5-minute interval between readings. Korotkov phase V was taken as the diastolic blood pressure. The mean of the two readings was taken

as the BP. The waist was measured as the narrowest circumference around the trunk between the costal margin and the iliac crests.³ The hips were taken to be the largest circumference between the waist and the thighs." Waist-hip ratio (WHR) was calculated. Height and weight were also taken and body mass index (BMI) was calculated according to the formula $BMI = \text{Weight (kg)} / \{\text{Height (m)}\}^2$.

At the third visit, anthropometric data and blood pressure were recorded and blood was taken for a fasting lipid profile. Compliance was assessed by counting the remaining sachets of the preparation. A history was also taken at each visit regarding any side effects of the treatment. The scheme of events is depicted in Figure 1.

Minolest® is manufactured by Sanacare and consists of 5.5g sachets. Each sachet comprised ispaghula husk 62.3%, guar gum 16.2%, glucomannan 0.65%, citric acid 4.6%, beta carotene 1.3%, aspartame 0.65%, natural orange flavour 1.3% and potato starch 13%. The placebo was also formulated by Sanacare and comprised identical 5.5g sachets with Maltodextrin C*Pur 1908 79.2%, citric acid 3%, beta carotene 1.3%, aspartame 0.5%, natural orange flavouring 1% and Pregeflo P250 15%.

Statistical Analysis

Statistical analysis was performed using the PC version of Minitab Release 10 for Windows (Minitab Inc. PA). HDL-C was logarithmically transformed to reduce skewness. Subsequently, the results were back transformed to the original units. Between group comparisons were carried using the two sample Student's t-test when normalisation could be achieved. Parameters that could not be normalised were compared using the Mann-Whitney U method. Parameters before and after treatment were compared using the paired Student's t-test.

Subject Characteristics

Eighty-three subjects met the entry criteria and were recruited for the treatment phase. Seven subjects defaulted follow up, 2 in the active treatment group and 5 in the placebo group. During the run-in phase, 9 subjects experienced a fall in the total cholesterol level to below the cut off of 5.2 mmol/l. These subjects (5 in the active treatment group and 4 in the placebo group) were excluded from the final analysis. Data for 67 subjects were used.

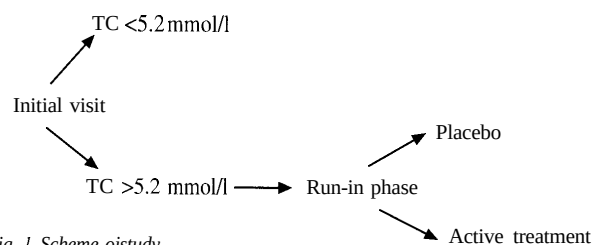


Fig. 1. Scheme of study

The characteristics of the two treatment arms are shown in Table I. The two groups were well matched for age, BMI and WHR. They did not differ significantly in TC, TG or HDL-C levels but LDL-C levels were significantly lower in the placebo group.

Results

The effects of Minolest® on the lipid profiles of our patients are shown in Figure 2. Sixty-seven subjects completed all three visits, 32 in the placebo group and 35 in the active treatment group. When analysed on an intention to treat basis, the results showed a significant decrease of both TC and LDL-C in the active treatment group but no significant change in either of these lipid levels in the placebo group. TC declined by 0.23 ± 0.53

TABLE I: BASELINE CHARACTERISTICS OF TREATMENT AND PLACEBO GROUPS

	Active treatment (mean $\pm$ SD)	Placebo (mean $\pm$ SD)
Age (years)	41.17 $\pm$ 8.7	37.31 $\pm$ 7.89
Male:female	14:21	13:19
Mean arterial pressure (mmHg)	98.56 $\pm$ 14.08	102.5 $\pm$ 11.72
Number of smokers	3	2
Body mass index (kg/m ²)	22.18 $\pm$ 2.66	23.15 $\pm$ 3.69
Waist-hip ratio	0.81 $\pm$ 0.07	0.81 $\pm$ 0.06
*Total cholesterol (mmol/l)	6.1 (5.43-8.06)	5.84 (5.32-8.38)
*Triglyceride (mmol/l)	1.54 (0.56-4.19)	1.47 (0.69-11.0)
HDL-cholesterol (mmol/l)	1.32 $\pm$ 0.43	1.15 $\pm$ 0.33
**LDL cholesterol (mmol/l)	4.12 (3.10-6.27)	3.87 (2.46-5.14)

HDL-cholesterol: high density lipoprotein cholesterol;

LDL-cholesterol: low density lipoprotein cholesterol

* Comparison by Mann-Whitney U method. Data represented as geometric mean (range)

** Difference between groups $P < 0.05$, comparison by Mann-Whitney U method. Data represented as geometric mean (range)

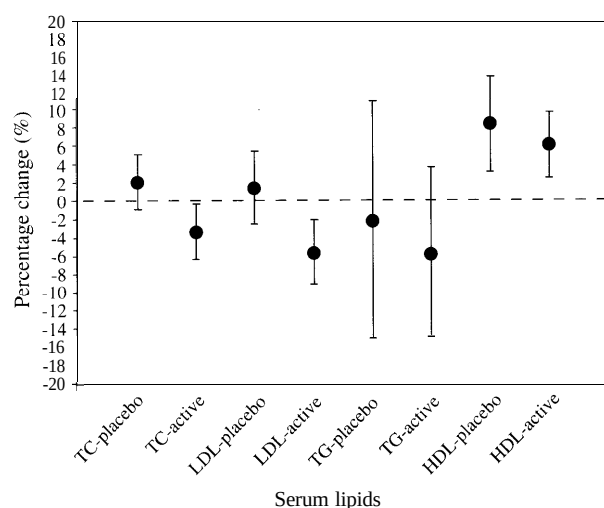


Fig. 2. Percentage change in serum lipids (mean and 95% confidence levels) in active treatment and placebo groups.

mmol/l (mean $\pm$ SD), P value = 0.026. LDL-C declined by a greater quantity of 0.24 ± 0.46 mmol/l, P value = 0.0057. The percentage fall in LDL cholesterol averaged $5.36 \pm 10.48\%$, P value = 0.008. The serum TG was not significantly altered in either active treatment nor placebo groups. BMI, weight, WHR and mean arterial pressure also remained unchanged. Interestingly, HDL-C was significantly increased in both the placebo and treatment groups (0.1 mmol/l and 0.09 mmol/l, respectively, $P < 0.01$). Comparisons of the lipid profiles between active treatment and placebo groups after treatment are shown in Table II. No detectable difference was seen in the final lipid profiles between the groups.

When only those subjects that took at least 50% of allocated sachets are considered, the percentage decrease of TC in the active treatment group was greater (4.61%, $P = 0.002$). The percentage decrease in total cholesterol and LDL cholesterol increased to 7.16% ($P = 0.001$) in the active treatment group. This increased further to 7.37% in the group that took more than 70% of the sachets ($P = 0.006$). In the placebo group, neither TC nor LDL-C was significantly different after treatment when compared to levels before treatment. This effect of compliance on the magnitude of change in LDL-C is demonstrated in Figure 3.

Compliance was generally poor but similar in both the placebo and active treatment groups. Only 78% of the placebo group and 77% of the active treatment group took 50% or more of the allocated 270 sachets. Most subjects cited inconvenience of taking the preparation as the reason for non-compliance. Few subjects reported side effects. Only 9 subjects (5 in the placebo group and 4 in the active treatment group) reported flatulence or abdominal discomfort and only 2 subjects abandoned the study as a consequence of side effects. Both the subjects who discontinued the treatment returned for follow up and were included in the analysis.

Discussion

In 1972, Trowel¹ proposed that dietary fibre was useful in the treatment of hyperlipidaemia.⁴ Since then, much animal and human work has been done. In essence, it has

TABLE II: LIPID PROFILES OF TREATMENT AND PLACEBO GROUPS AT THE END OF THE TRIAL

	Active treatment (mean $\pm$ SD)	Placebo (mean $\pm$ SD)	P value
*Total cholesterol (mmol/l)	5.93 (5.25-8.05)	5.84 (5.02-8.09)	0.55
*Triglyceride (mmol/l)	1.39 (0.60-3.08)	2.00 (0.65-11.5)	0.07
HDL-cholesterol (mmol/l)	1.47 $\pm$ 0.5	1.31 $\pm$ 0.38	0.12
*LDL cholesterol (mmol/l)	3.98 (2.84-6.3)	3.92 (2.16-5.54)	0.663

* Comparison by Mann-Whitney U method. Data represented as geometric mean (range)

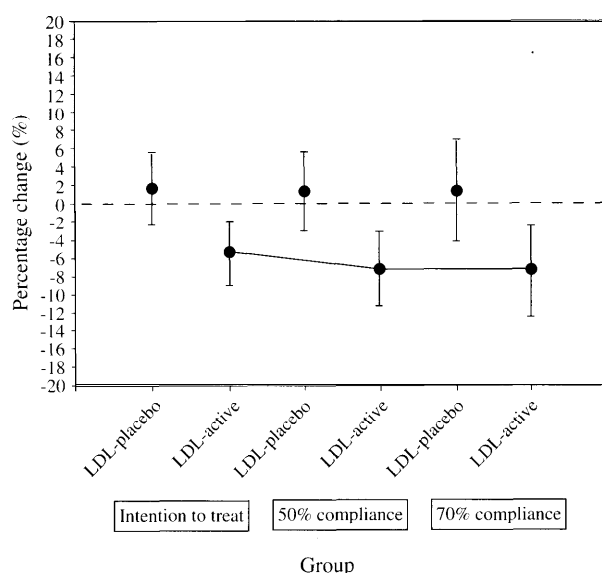


Fig. 3. Percentage change in low-density lipoprotein cholesterol level (mean and 95% confidence levels) according to compliance

been found that ingestion of large quantities of the soluble fibres (pectin, guar gum, psyllium, oat bran) has a beneficial effect on the total cholesterol level and the LDL cholesterol level in humans, lowering levels from 5% to 20% depending on the study.

Guar gum is the most widely studied of the soluble fibres. It is a galactomannan derived from the seed of the leguminous plant *Cyanopsis tetragonoloba* and is used in the food industry as a thickening agent. It has been shown that the addition of guar gum to the diet, lowers serum TC and LDL-C.⁵ Psyllium is a polysaccharide based on arabinose and galacturonic acid units and is derived from *Plantago ovata* (Ispaghula). This too has been shown to have a cholesterol lowering effect but to a lesser extent than guar gum.^{6,7} In general, the studies do not show any effect on TG and HDL-C.

The cholesterol lowering effect is poorly understood. The theory that soluble fibres bind bile salts and interfere with the enterohepatic circulation of bile acids has received the most attention. This would be consistent with the results of studies which have demonstrated increased in the fractional clearance rate of cholesterol in patients treated with dietary soluble fibre.^{5,8} Psyllium has also been shown to increase the bile acid pool in hypercholesterolaemic men.⁹ Other authors have suggested that it may be the viscosity of the dietary fibre that is important in lipid lowering by impairing the diffusion of nutrients through the unstirred water layer in the gut.^{10,11} Glucomannan, one of the most viscous soluble fibres¹¹ may thus have a beneficial effect in this preparation.

In the intention to treat analysis for this study, the decrease in TC is small but statistically significant. The magnitude of the decrease is slightly higher when the

analysis is limited to those that took 50% or more sachets suggesting that increased compliance may give rise to greater cholesterol lowering. There appears to be greater impact on the LDL-C level than on the TC and this is due to the fact that, along with the fall in TC, there is a significant rise in the HDL-C level in both groups. The change in LDL-C level appears to be similarly affected by compliance. Furthermore, the TC and LDL-C levels tended to show an increase in the placebo group although this did not reach statistical significance. This leads us to suggest that subjects may have been more indiscriminate with their diet, perhaps lulled into a false sense of security by the ingestion of the fibre preparation. If this were so, the magnitude of decrease in the active treatment group may have been made smaller by similar dietary indiscretion. This is consistent with previous studies that have shown that dietary fibre has the greatest effect on the lipid profile when combined with a low fat diet.

The increase in HDL-C is seen in both the placebo and treatment groups and as such, is not related to the ingestion of fibre. The authors are unable to explain this increase in HDL-C except to suggest that this could have been the result of some lifestyle change (e.g. exercise) that our questionnaire was insufficiently sensitive to detect.

The failure of dietary fibre to influence levels of TG has been documented previously.¹² The results also confirm that body weight and BMI are unchanged by treatment.

Conclusion

Minolest® is a useful adjunct to dietary and lifestyle modification in normal hypercholesterolaemic subjects, producing a favourable effect on the coronary artery disease risk profile of subjects, lowering TC, LDL-C and raising HDL-C. The change is small, however, and this form of treatment should not be advocated for those with very elevated lipid levels or at significant risk of coronary artery disease. For these situations, very powerful drugs, such as the statins, are available which have a much greater lipid lowering effect.

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