A double-blind study to evaluate the safety and efficacy of policosanol vs. atorvastatin in the treatment of hyperlipidaemia

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INTRODUCTION

Policosanol is a mixture of fatty alcohols derived from natural sources including beeswax, a waxy extract of sugarcane and rice bran. The components of policosanol include 1-octacosanol, 1-dotriacontanol, 1-tetracosanol, 1-tetratriacontanol, 1-hexacosanol, 1-heptacosanol and 1-nonacosanol.

Effects on cholesterol metabolism and antioxidant effects that prevent the oxidation of LDL-cholesterol, are reported to be responsible for the healthful effects of policosanol. Policosanol was shown to be effective in lowering both total cholesterol and low-density lipoprotein (LDL) cholesterol, the 'bad' cholesterol, and to increase levels of the 'good' type of cholesterol, high-density lipoprotein (HDL) cholesterol. Other beneficial effects include inhibition of platelet aggregation, which in turn is helpful in maintaining cardiovascular health. A comparative study with the commonly used statin drug Lovastatin in subjects suffering from intermittent claudication revealed the superior benefits of policosanol.

Policosanol is reported to prevent oxidation of LDL and the related detrimental actions of metalloproteinase enzymes. Metalloproteinase enzymes promote blood vessel destruction, partly by interfering with HDL's protective effect (1). Studies report that rats treated with policosanol show fewer foam cells, reflecting modulated inflammatory response and higher blood vessel integrity (2). Another reported action of policosanol is its ability to reduce the proliferation of cells in the lining of the arteries (3). Policosanol's ability to stop cell overgrowth was described by the authors of that study as being in agreement with the anti-proliferative effects reported for other lipid lowering drugs, such as most of the statins (4).

Policosanol also inhibits the formation of clots, and may work synergistically with aspirin in this respect (5). A related effect is that significant reductions in the level of thromboxane occur in humans after two weeks of policosanol (6). Thromboxane is a blood vessel-constricting agent that contributes to abnormal platelet aggregation that can cause a heart attack or stroke.

CLINICAL VALIDATION: EXAMPLES OF CONTRADICTORY RESEARCH REPORTS

In a randomized, double blind study published in the *International Journal of Clinical Pharmacological Research*, doctors investigated the efficacy and tolerability of policosanol at doses of 20 mg a day compared with 40 mg a day (7). Patients with high cholesterol had been on a cholesterol-lowering diet, but failed to achieve desired results. The patients were instructed to continue the cholesterol-lowering diet and were allocated to receive either placebo, policosanol 20 mg/day, or 40 mg/day.

After 28 weeks, policosanol at 20 and 40 mg/day lowered LDL-cholesterol by 27.4% and 28.1%, while total cholesterol was reduced by 15.6% and 17.3% respectively. Most impressive was the finding that beneficial HDL cholesterol was increased by 17.6% in the 20 mg/day and 17% in the 40 mg/day policosanol groups. There were no significant changes in the placebo group.

The conclusion of this study was that

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20 mg a day of policosanol provides about the same cholesterol-lower efficacy as 40 mg a day. Consistent with previous studies, no adverse effects were observed. High levels of HDL cholesterol may be the most important factor in protecting against cholesterol induced arterial disease (8). It is the HDL molecule that removes plaque from arterial walls (9). Scientific studies show that people with the highest levels of HDL cholesterol have the greatest longevity (10).

In another recent study, the effects of policosanol were measured on menopausal women in a randomized, double blind, multi-center placebo-controlled trial (11). These women showed elevated total and LDL-cholesterol despite a six-week standard lipid-lowering diet. Eligible patients were randomized to receive placebo or policosanol 5 mg/day for eight weeks and the dose was doubled to 10 mg/day during the next eight weeks. Results determined that policosanol at doses of 5 and 10 mg/day significantly decreased LDL-cholesterol (12.9%, 26.7%), total cholesterol (12.9%, 19.5%), LDL-cholesterol / HDL-cholesterol (17.2%, 26.5%) and total cholesterol / HDL-cholesterol (16.3%, 21.0%) when compared with baseline and placebo. The study concluded that policosanol was effective in hypercholesterolemic postmenopausal women.

There have however been some clinical studies that show policosanol is ineffective. Many of these studies that show policosanol to be unsuccessful are done in Caucasian subjects of European descent. Many of the successful clinical studies have been based in Cuba (12). Importantly though, all of these studies found that policosanol was well tolerated and had no adverse events associated with its use. One such study used authentic Cuban sugar cane policosanols in healthy hyper-cholesterolemic volunteers for a period of 28 days. The results of the study showed no affect on plasma lipid values, no difference between treatment and control groups in plasma total, LDL-, HDL-cholesterol, and triacylglycerol concentrations (13). Another clinical study found that Policosanol (20 mg/d for 12 weeks) did not significantly alter plasma total cholesterol, LDL-C, high-density lipoprotein cholesterol, or triglyceride levels when judged against baseline values or with values of the placebo group (14). Atorvastatin given 10 mg/d for 12 weeks decreased total cholesterol by 27% and LDL-C by 35%. Policosanol combined with atorvastatin failed to result in any further reduction in lipid levels compared to atorvastatin alone.

CURRENT STUDY REVEALS CLINICAL EFFICACY OF NON-CUBAN SUGARCANE POLICOSANOL

A recent study conducted in India with subjects of South Asian origin revealed beneficial effects of policosanol in lipid levels and inflammatory markers. Policosanol (15 mg/day) was compared to Atorvastatin (10 mg/day) in a randomized, double-blind study on 40 patients with hypercholesterolaemia (Type IIa) mixed dyslipidemia (Type IIb) and/or primary hypertriglyceridemia for 24 weeks. Policosanol compared favorably with Atorvastatin at improving the serum lipid profile. All the 40 subjects completed the study implying that both the groups benefited positively.

MATERIALS AND METHODS

A summary of the clinical protocol is presented in Table I. 40 patients of either sex, above 18 years of age and below 65 years of age, suffering from hypercholesterolaemia (Type IIa) mixed dyslipidemia (Type IIb) and/or primary hypertriglyceridemia were identified. Only patients with primary hyper-cholesterolaemia (Type IIa) mixed dyslipidaemia (Type IIb) or primary hypertriglyceridaemia (LDL cholesterol≥160 mg/dl and or triglycerides>200 mg/dl) were enrolled in the study.

Table I – Study protocol

Procedure	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Informed consent	X						
Inclusion / Exclusion	X						
Demographics	X						
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
LABORATORY TESTS							
Hb	X						X
ESR	X						X
TC	X						X
DC	X						X
Lipid profile	X		X		X		X
Liver function test	X						X
Renal function test	X						X
Adverse events		X	X	X	X	X	X

Patients were excluded due to the following reasons: pregnancy / lactation, rossly abnormal liver, kidney or hematological abnormalities, secondary hyperlipidaemia apart from diabetes mellitus or hypothyroidism, and patients enrolled in any other clinical trials in the last 3 months. The patients who were already on cholesterol reducing agents had a 1-week wash out period before being included in the study. Patients were included only if they did not have any exclusion criteria as per the protocol. The informed consent was taken from every patient included in the study. All biochemical, hematology and urine analysis tests showed no abnormalities that imply clinical significance.

At the baseline visit, patients were assessed for demographic and baseline characteristics and also various lab tests – Hematological parameters, Lipid and Renal profile, Liver function tests – and concomitant treatment (Table II). Patients were then randomized according to the randomization list into either of the treatment groups. These lab tests were subsequently assessed at the end of week 24.

The patients received oral medication of 15 mg of Policosanol or Atorvastatin (10 mg) capsule daily before bed time for 24 weeks. Hepatic synthesis of cholesterol is thought to occur primarily at night, thus once daily doses of Policosanol were given in the evening. Administration of the study medication was supervised by the investigator or a designate. The

Table II – Various haematological and biochemical parameters investigated during the course of study

Hematological parameters	Liver Function test	Renal Function test	Other tests
Hb	Total bilirubin	Creatinine	Apo-A1
RBC	Direct bilirubin	Uric acid	Apo B
PCV	Indirect bilirubin	Phosphorus	Lipo (a)
MCH	Total protein	BUN	hs-CRP
MCV	Albumin		
MCHC	Globulin		
RDW	SGPT		
WBC	SGOT		
Platelets	Alkakine phosphatase		
ESR	GGT		

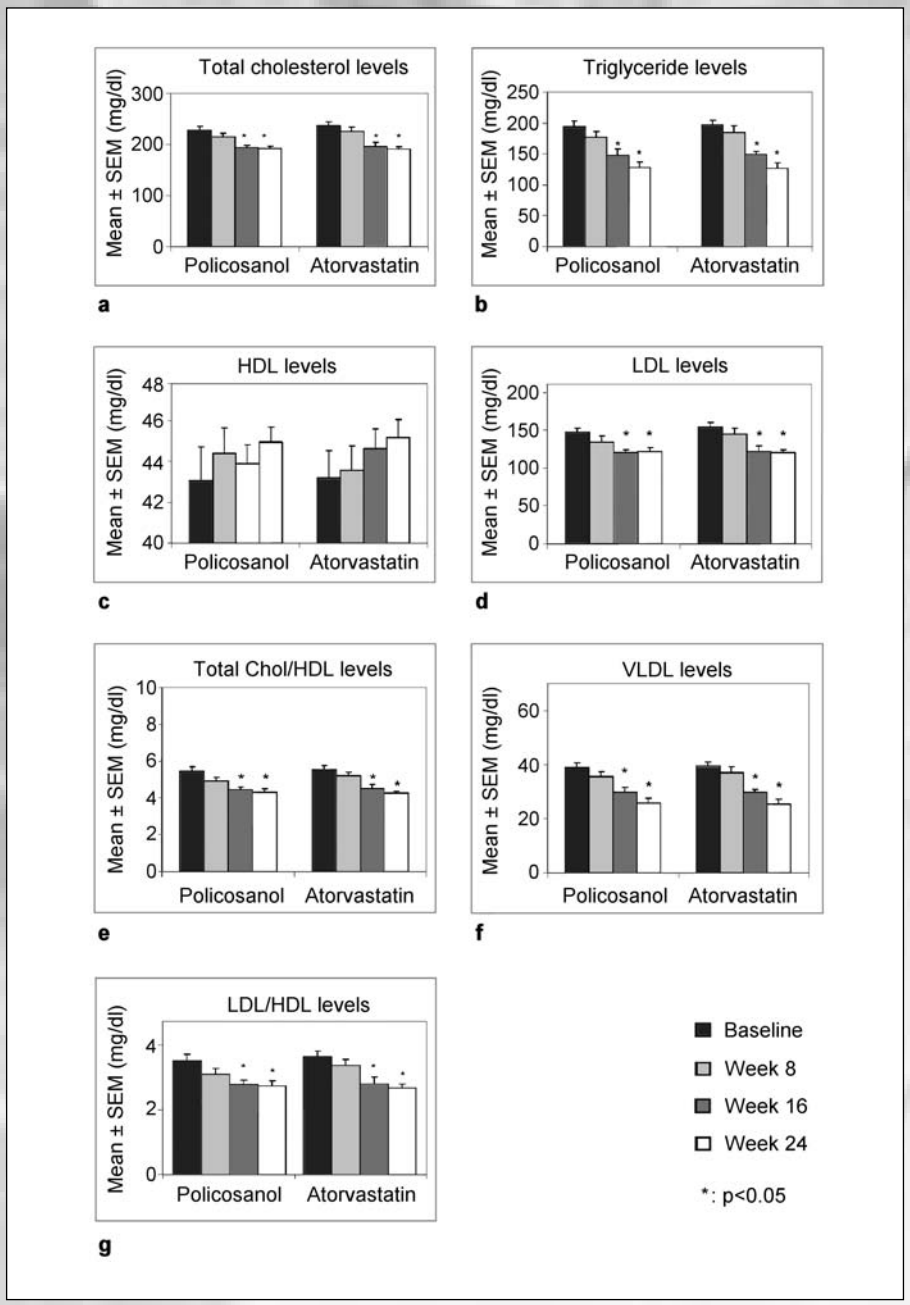

Figure 1 – Comparative effects of policosanol and atorvastatin on serum lipoprotein levels

study duration was for a period of 24 weeks.

The schedule of visits of each patient was as follows:

Visit 0	Week 0
Visit 1	Week 4
Visit 2	Week 8
Visit 3	Week 12
Visit 4	Week 16
Visit 5	Week 20
Visit 6	Week 24

During these visits the signs, symptoms and adverse effects if any were recorded. The protocol was repeated at all follow-up visits.

RESULTS

Treatment with Policosanol (15 mg/day) for 24 weeks in a double blind study to patients suffering from primary hypercholesterolemia (Type IIa), mixed dyslipidaemia (Type IIb) or primary hypertriglyceridaemia resulted in a decrease in Total Plasma Cholesterol levels (17.76%, p<0.0001), Plasma Triglyceride levels (33.87%, p<0.00001), Low Density Lipoprotein (LDL) levels (20.51%, p<0.004), Very Low Density Lipoprotein (VLDL) levels (33.87%, p<0.00001) (Figure 1a, 1b, 1d, 1e) as compared with treatment of patients with Atorvastatin (10 mg/day). HDL levels were enhanced favorably in both groups (Figure 1c).

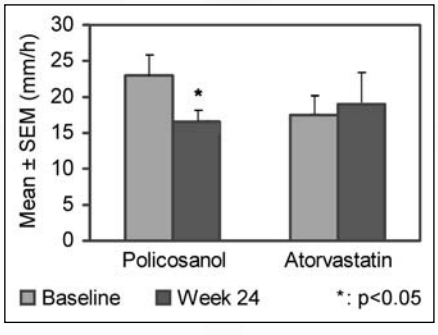

Figure 2 – Comparative reduction in ESR levels in treatment groups

Atorvastatin usage resulted in reductions of Total Plasma Cholesterol (19.56%, p<0.00001), Plasma Triglyceride (35.53%, p<0.00001), Low Density Lipoprotein (LDL) (23.13%, p<0.0002), and Very Low Density Lipoprotein (VLDL) (35.53%, p<0.00001) levels as compared to initial base line lipid levels at the end of 24 weeks. The High Density Lipoprotein (HDL) cholesterol levels increased by 9.90% and 7.73% respectively for Policosanol and Atorvastatin treated groups.

Siginificant reduction in LDL/HDL and TC/HDL ratios on treatment with Policosanol and Atorvastatin (24.56% vs. 26.17% and 21.57% vs. 22.86%) was observed. Almost similar results were observed in both treated groups suggesting that Policosanol is equally effective in bringing about a reduction in the lipid levels in comparison with Atorvastatin-treated groups.

Significant decrease in the ESR (erythrocyte sedimentation rate), an early marker of inflammation in Policosanol treated group (29.32%, p<0.034) in comparison to a non-significant decrease in the Atorvastatin-treated group (18.38%) was observed (Figure 2).

hs-CRP (high sensitivity C-reactive protein), a useful indicator of major tissue damage and Coronary Heart Disease (CHD), was also investigated. A reduction in hs-CRP levels was observed in both Policosanol and Atorvastatin treated groups (36.33% vs 22.95%). Thus Policosanol was more effective than Atorvastatin in reducing the hs-CRP levels (Figure 3).

An improvement in the liver function test, represented by a decrease in the SGOT (serum glutamic oxaloacetic transaminase) levels in the Policosanol treated group (18.38%, p <0.023)) in comparison with the Atorvastatin treated group (14.07%) was observed.

Apolipoprotein B is composed of over 90% of low density protein (LDL) particles which solubilizes cholesterol within the LDL complex, which increases the transport capacity of LDL for subsequent deposit on the arterial wall. Apo B is a convenient marker for assessing the cholesterol depositing capacity and is a better discriminator of

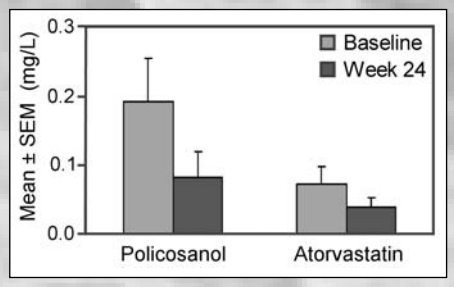

Figure 3 – Comparative reduction in hs-CRP levels in treatment groups

angiographically documented coronary artery disease than LDL cholesterol. The reduction in Apo B levels in Policosanol treated group was 5.66% in comparison to the Atorvastatin treated group, which was 13.47% (significant at $p<0.03$) .

Significant reduction in Uric acid levels was also observed in Policosanol and Atorvastatin treatment groups (14.09 and 20.10%, significant at $p<0.01$ and 0.005). No drug related toxicity symptoms were observed on treatment with Policosanol in the study duration.

DISCUSSION

There are various policosanol sources. The well researched Cuban policosanol mixture (CPC) is made of many cosanols (long-chain aliphatic alcohols), derived from the waxy fraction of sugar cane. Other policosanol sources include wheat, rice bran, beeswax, sorghum and flax waste stream (15-18).

Initial promising research involving policosanol was conducted in Cuba with study populations comprising mostly subjects from Central and South America of Latino descent. A review in 2002 in a medical journal described policosanol as a "fascinating new agent for the prevention and treatment of atherosclerotic disease" (19). A subsequent review (2005) reported CPC (Cuban policosanol) to have superior hypolipidaemic activity when compared with phytosterols and stanols (20).

Studies on non-CPC policosanol have suggested that this type of policosanol does not have hypolipidaemic activity. A randomised controlled trial involving 60 normo- to mildly hyperlipidaemic subjects received 20 mg/day of wheat germ-derived policosanol for four weeks and showed no changes in blood lipids (21). Another randomised controlled trial using a rice-derived policosanol showed that total cholesterol fell only by 5% in the policosanol group, with no changes in LDL or HDL cholesterol, C-reactive protein or total homocysteine (22). Subjects participated in an eight-week run-in phase with an American Heart Association Step I diet, then were administered 10 mg policosanol or placebo for eight weeks. Most recently, a randomised controlled trial from South Africa that examined the hyperlipidaemic effect of sugar-cane wax policosanol in 19 hyperlipidaemic subjects demonstrated that it was no different from the placebo (23).

All earlier promising research done using CPC mixture was performed in Cuba. However, two recent clinical trials using CPC done outside of Latin America have yielded similar results to non-CPC policosanol. A randomized study in Canada involved 21 hyperlipidaemic men and women, who were given placebo or 10 mg policosanol for 28 days. Results showed that there were no significant changes in the blood-lipid parameters (24). The second study, published in the *Journal of the American Medical Association*, was a dose-escalation randomized controlled trial involving 143 hyperlipidaemic men and women (25). Subjects completed a run-in diet phase and then received 10, 20, 40 or 80 mg/day policosanol or placebo. Results showed there were no significant changes in the lipid parameters in any group.

The present study however revealed that non-CPC policosanol (derived from sugarcane grown in India) was effective in beneficially influencing serum lipid levels and related parameters in hyper-cholesterolemic subjects of South Asian origin, and compared favorably with Atorvastatin in improving the serum lipid profile.

Policosanol was well tolerated and no drug-related adverse drug reactions were observed. It is concluded that Policosanol is a safe and effective supplement for lowering of LDL, triglycerides and VLDL levels with high degree of safety and can be used to lower several cardiovascular disease risk factors.

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