Single Blind Placebo Controlled Randomized Trial on Hypolipidemic Effects of Nicotinic Acid

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ABSTRACT

The research study was planned to observe effects of Nicotinic acid (niacin) on blood pressure, body weight, bad cholesterol; i.e. LDL-cholesterol and good cholesterol; i.e. HDL-cholesterol. It was single blind placebo-controlled research study, which was conducted at Jinnah Hospital, Karachi, from April 2008 to December 2008. Forty male and female hyperlipidemic patients were included in the research study, among which 20 patients were on placebo as control group, and 20 were on tablet Niacin, 2.25 grams daily, in divided doses for the period of three months. Patients with diabetes mellitus, peptic ulcer, renal disease, hepatic disease, hypothyroidism and alcoholism were excluded from the study. Body weight and blood pressure of patients were recorded at fortnightly visit. LDL-Cholesterol was calculated by Friedwald formula (LDL=TC-(TG/5+HDL-C). Serum HDL-cholesterol was determined by direct method. Serum cholesterol and triglycerides were estimated by the enzymatic calorimetric method. Data regarding results were expressed as the mean ± SD and "t" test was applied to determine statistical significance of results. A probability value of <0.05 was the limit of significance. Three patients were dropped from the study due to side effects of Niacin. In three months of treatment with 2.25 grams of niacin HDL-cholesterol increased from 36.41±1.96 to 43.70±1.81 mg/dl, which was highly significant change when analyzed statistically. Niacin has decreased LDL-Cholesterol from 182.58±8.74 mg/dl to 119.29±4.08 mg/dl, which was highly significant (P<0.001), when compared statistically by paired "t" test. Overall percentage (%) changes from day-0 to day-90 were 34.66. Triglycerides reduced from 169.64±7.60 to 137.35±6.31 mg/dl, which was highly significant (P value <0.001) reduction in three months. Niacin has also reduced Blood Pressure. Difference between mean values of systolic and diastolic blood pressure at day-0 and day-90 were found highly significant (P<0.001). Body weight was reduced from 66.29±194 kg to 64.79±1.82 kg in three months. This change was significant (P<0.01). We concluded from the research study that niacin decreases blood pressure, body weight and LDL-Cholesterol and increases HDL-cholesterol in primary hyperlipidemic patients.

Key words: Nicotinic acid, low density lipoprotein cholesterol, high density lipoprotein cholesterol,

INTRODUCTION

Nicotinic acid (niacin) has an effect on blood vessels, allowing them to relax, thus allowing better blood flow to all regions of the body, including hands and feet. Inositol hexaniacinic acid is one form of niacin that can have this kind of effect on the circulatory system. As compared to its recommended daily allowance (RDA), much high doses of Nicotinic acid (niacin) are used to prevent development of atherosclerosis and to reduce recurrent complications like heart attack,myocardial infarction and peripheral vascular disease.[1-2] Circulation disorders are painful and often debilitating problems. Intermittent claudication is a circulation disorder characterized by painful cramping in the calf region, usually brought on by walking. Another aggravating disease caused by poor circulation is Raynaud's disease, causing pain and numbness in the extremities when exposed to cold. The combination of niacin and a cholesterol-lowering drug called simvastatin (which belongs to a class known as HMG-CoA reductase inhibitors or statins) do dramatically slow the progression of heart disease, reducing risk of heart attack leading to death. Niacin is commonly used to lower elevated LDL-cholesterol and triglyceride levels in the serum and is more effective in increasing HDL-cholesterol levels. A high level of LDL in the blood may mean that cell membranes in the liver have reduced the number of LDL receptors due to increased amounts of cholesterol inside the cell. After a cell has used the cholesterol for its chemical needs and doesn't need any more, it reduces its number of LDL receptors.

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This enables LDL levels to accumulate in the blood. When this happens, the LDLs begin to deposit cholesterol on artery walls, forming thick plaques. In contrast, the HDLs--the "good" guys--act to remove this excess cholesterol and transport it to the liver for disposal.[3-4] High doses of Nicotinic acid (niacin) have been shown to raise HDL-cholesterol, and lower LDL-cholesterol and triglycerides.[5] Nicotinic acid, but not the Nicotinamide, has been observed to have substantial benefits in lowering high cholesterol levels. It is particularly effective in raising levels of high-density lipoprotein (HDL) levels, but it is less effective to decrease low-density lipoprotein (LDL) levels than some other cholesterol-lowering drugs. Nicotinic acid is currently used as one of the first-line treatment of hyperlipidemia either alone or in combination with HMG-CoA reductase inhibitors.[6-9]

MATERIAL & METHODS

Place of research conduction was Jinnah Hospital Karachi and duration of study was 3 months, starting from April 2008 to December 2008. 40 patients of primary hyperlipidemia were enrolled for the research, selected from ward and OPD of Jinnah Hospital, Karachi. Male and female primary hyperlipidemic patients of 17 to 70 years age were selected. Patients with alcohol addiction, hypothyroidism, peptic ulcer, diabetes mellitus, renal disease, hepatic disease, were excluded from the study. Written consent was obtained from all participants. Research study was started after approval by Research Ethics Committee, Jinnah Hospital, Karachi. The study period consisted of 90 days with fortnightly follow up visits. The required information like name, age, sex, occupation, address, previous medication, date of follow up visit and laboratory investigations, etc of each patient was recorded on a proforma, especially designed for this study. Initially a detailed medical history and physical examination of all patients were carried out. All the base line assessments were taken on the day of inclusion (Day-0) in the study and a similar assessment was taken on Day-90 of research design. After fulfilling the inclusion criteria patients were randomly divided into two groups, i.e.Drug-1(tab: Niacin 2.25gm) and Drug-2 (placebo capsules, containing equal amounts of partly grinded wheat) groups. Patients of drug-1 group were advised to take Tab: Niacin (250 mg), half tablet thrice daily, after meal for 2 days, then by increasing the dose one tablet, TID, after meal for 2 days, then 2 tablets, thrice daily after meal for 2 days, then the maintenance dose of 3 tablets, thrice daily, till end of the study period, i.e. up to day-90. This regimen of dose of drug (called titration of Niacin) was applied due to avoidance of it's adverse effects produced by starting with higher doses of the Niacin.17 Patients of drug-2 group were provided placebo capsules, i.e. three capsules, TID, after meal for 90 days. Patients were called every 2 weeks for follow up to check blood pressure, weight, pulse rate and general appearance of the individual. Drug compliance to the regimen was monitored by interview and counseling at each clinical visits. Data were expressed as the mean ± SD and "t" test was applied to determine statistical significance as the difference. For non significant results P-value >0.05 was used and for significant to highly significant results P-value <0.01 and <0.001 was used in the research. Serum LDL-cholesterol was calculated by Friedwald formula (LDL-Cholesterol = Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol)[8].

RESULTS

Three patients discontinued to take drug in group-1 (Niacin group) due to side effects of the drug like flushing, sensation of heat, and headache. So, out of forty, 37 patients completed the study period that was three months. Table showing base line and post treatment values is self explanatory. When results were summed up and test parameters were compared, it was seen that, after three months of treatment with niacin, LDL-cholesterol decreased from 182.58±8.74 mg/dl to 119.29±4.08 mg/dl, which is highly significant (P<0.001). The overall percentage change from day-0 to day-90 was -34.66. In placebo group at day-0, LDL-cholesterol level was 150.75±2.67 mg/dl, which decreased to 148.80±2.28 mg/dl, which is non-significant (P>0.05).The overall percentage decrease in the parameter was -1.29. The difference between mean values among placebo group and Niacin group is 33.4, which is highly significant (<0.001) as shown in the table 3. Niacin has increased HDL-cholesterol from 36.41±1.96 to 43.70±1.81 mg/dl, which is highly significant change (P-value <0.001). In percentage it is 20.02% increase. Triglycerides reduced from 169.64±7.60 to 137.35±6.31 mg/dl, which was highly significant (P value <0.001) reduction in three months. Systolic blood pressure reduced from 125.88±3.48 mm of Hg to 119.70±3.13 mm of Hg in three months. Diastolic blood pressure reduced from 89.11±1.92 to 84.70±1.74 mm of Hg in this duration of treatment with 2.25 grams of Niacin. These changes in both, systolic and diastolic blood pressure are highly significant (P<0.001). Body weight reduced from 66.29±1.94 kg to 64.79±1.82 kg, which is also highly significant (P<0.001) when compared with placebo group.

Table 1: Difference of effects of drug on body weight, systolic, diastolic blood pressure, LDL and HDL-Cholesterol between placebo and niacin group of patients in 3 months of treatment.

Placebo Group (n=20)				Drugs Group (n=17)			
Parameter	**Pre-treatment**	**Post-treatment**	**P Value**	**Pre-treatment**	**Post-treatment**	**P Value**	**Difference in groups**
Body weight	69.35±1.76	69.17±1.68	>0.05	66.29±1.94	64.79±1.82	<0.001	2.01%
Systolic BP	122.75±219	120.75±2.18	<0.01	125.88±3.48	119.70±3.13	<0.001	3.28%
Diastolic BP	84.25±1.99	82.00±1.82	<0.01	89.11±1.92	84.70±1.74	<0.001	2.27%
LDL-C(mg/dl)	150.75±2.67	148.80±2.28	>0.05	182.58±8.74	150.41	<0.001	33.4%
TG	148.45±4.80	146.20±4.20	>0.05	169.64	±6.94	<0.001	17.52%
HDL-C mg/dl)	35.50±1.13	35.75±1.07	>0.05	±7.60	137.35	<0.001	19.32%
				36.41	±6.31		
				±1.96	43.70		
					±1.81		

Key:(Drug Group is on niacin 2.25 gm, ± indicates standard error of mean, BP stands for blood pressure, Body weight is measured in kilograms, blood pressure is measured in mm of Hg, P Value >0.05 indicates non significant, P Value <0.01 indicates significant, P Value <0.001 indicates highly significant, Figures in parentheses indicate number of patients)

DISCUSSION

Three patients discontinued treatment due to development of side effects like flushing, urticaria and sensation of heat in the body. Other patients were convinced for continuing therapy, by taking aspirin 250 mg, before taking 1st dose of niacin at morning, every day. There are various drug groups which are used as hypolipidemic agent and among all lipid lowering drugs, niacin appears to be the best HDL upraising and LDL lowering agent. In our research, HDL-cholesterol increased from 36.41±1.96 to 43.70±1.81 mg/dl and LDL-Cholesterol levels decreased by 34.66% in men and women with high LDL-C levels treated with 2.25 grams of Niacin. Reduction in body weight was 2.26%. Systolic blood pressure decreased 4.90% and diastolic blood pressure reduced 4.94% in three months of treatment with same dose of niacin as used in LDL lowering and HDL upraising dose. Triglycerides reduced from 169.64±7.60 to 137.35±6.31 mg/dl, which was highly significant (P value <0.001) reduction in three months. These results match with the results of study conducted by J. M. S. Lee et al[9] who observed almost same changes in LDL-Cholesterol, body weight and blood pressure. HDL-cholesterol is not increased as much as in our research study. Their research proved only 11.09% increase in HDL cholesterol. In their study LDL-C reduced 29.75%, systolic BP 2.89%, diastolic BP 3.98% and body weight 2.94%, in 90 days of treatment with three grams of niacin in 47 primary hyperlipidemic patients. Results of study conducted by Allen J. Taylor et al[10] also match with our study results. In their results LDL cholesterol reduced 31.98%, systolic blood pressure 3.87%, diastolic blood pressure 3.87% and body weight 2.91%. They observed remarkable increase in HDL cholesterol in 15 female hyperlipidemic patients when two grams of niacin was used for 4 months. Guyton JR[11] observed that niacin is very effective among all lipid lowering drugs, that can reduced LDL cholesterol and increase HDL cholesterol remarkably. They proved 30.12% reduction in low density lipoprotein cholesterol, 17% decrease in triglycerides and 20.56% increase in high density lipoprotein cholesterol when 3 grams of niacin was used in 20 hyperlipidemic patients for three months. These results also coincide with our results regarding LDL and HDL cholesterol. Results of research study conducted by Bays H E and McGovern ME[12] are in contrast with our results who observed only 12.99% decrease in LDL-Cholesterol by using three grams of niacin in 13 hyperlipidemic patients for the period of three months. In their observation systolic and diastolic blood pressure was reduced 0.19 and 2.51% respectively. Body weight was reduced 2.90%. These findings do not match with our results, except body weight. The reason for difference may be due to small sample size and environmental factors. Their patients strictly followed step-I diet, along with taking drug. Taylor AJ et al[13] proved 24.03% reduction in concentration of LDL cholesterol, 10.32% reduction in serum triglycerides and 11.87% increase in HDL cholesterol. Their observation is in contrast with our observation, probably due to small sample size and low dose of the drug in our study. They used 4.4 grams of niacin in 87 hyperlipidemic patients for the period of 8 months. F. A. Jaffer[14] used 2.5 grams of niacin in 30 hyperlipidemic patients for four months and observed 20% increase in HDL cholesterol and only 13% decrease in LDL cholesterol. Result of one of the parameter that is HDL cholesterol matches with our result but in another parameter that is LDL cholesterol results of his study and our research results are in contrast. The reason of this contrast may be the cases of secondary hyperlipidemia, they included in their study. We excluded secondary hyperlipidemic patients in our research work. In his study 10 patients discontinued to take part in

research as agreed initially. The reason for this remarkable dropout was urticaria, warmth feeling and redness on dependant parts of the body by taking niacin. Mechanism by which aspirin blocks niacin-induced flushing and feeling of hotness is explained by A. Muller et al.[15]

REFERENCES

1. K.Prasad. Flax Lignan Complex Slows Down the Progression of Atherosclerosis in Hyperlipidemic Rabbits**.** Journal of Cardiovascular Pharmacology and Therapeutics 2009; 14(1): 38 - 48.
2. L. Yvan-Charvet, J. Kling, T. Pagler, H. Li, B. Hubbard, T. Fisher, C. P. Sparrow, A. K. Taggart, and A. R. Tall. Cholesterol Efflux Potential and Antiinflammatory Properties of High-Density Lipoprotein After Treatment With Niacin or Anacetrapib**.** Arterioscler Thromb Vasc Biol 2010; 30(7): 1430 - 1438.
3. A L. Gould, J. Koglin, R. P Bain, C.-A. Pinto, Y. B Mitchel, R. C Pasternak, and A. Sapre. Effects of sources of variability on sample sizes required for RCTs, applied to trials of lipid-altering therapies on carotid artery intima-media thickness. Clinical Trials 2009; 6(4): 305 - 319.
4. B. J. Wu, L. Yan, F. Charlton, P. Witting, P. J. Barter, and K. A. Rye. Evidence That Niacin Inhibits Acute Vascular Inflammation and Improves Endothelial Dysfunction Independent of Changes in Plasma Lipids**.** Arterioscler Thromb Vasc Biol 2010; 30(5): 968 - 975.
5. G.S.Goumas. Is There Evidence-based Hypolipidemic Treatment With Clinical Benefit Beyond Statins? Angiology 2009; 60(1): 93 - 98.
6. W. R. Hiatt, A. T. Hirsch, M. A. Creager, S. Rajagopalan, E. R. Mohler, C. M. Ballantyne, J. G. Regensteiner, D. Treat-Jacobson, and R. A. Dale. Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery diseaseVascular Medicine 2010; 15(3): 171 - 179.
7. J. K. Duggal, M. Singh, N. Attri, P. P. Singh, N. Ahmed, S. Pahwa, J. Molnar, S. Singh, S. Khosla, and R. Arora. Effect of Niacin Therapy on Cardiovascular Outcomes in Patients With Coronary Artery Disease**.** Journal of Cardiovascular Pharmacology and Therapeutics 2010; 15(2): 158 - 166.
8. S. A. Sorrentino, C. Besler, L. Rohrer, M. Meyer, K. Heinrich, F. H. Bahlmann, M. Mueller, T. Horvath, C. Doerries, M. Heinemann, *et al.* Endothelial-Vasoprotective Effects of High-Density Lipoprotein Are Impaired in Patients With Type 2 Diabetes Mellitus but Are Improved After Extended-Release Niacin Therapy Circulation 2010; 121(1): 110 - 122.
9. J. M.S. Lee, M. D. Robson, L.-M. Yu, C. C. Shirodaria, C. Cunnington, I. Kylintireas, J. E. Digby, T. Bannister, A. Handa, F. Wiesmann, et al. Effects of high-dose modified-release nicotinic Acid on atherosclerosis and vascular function a randomized, placebo-controlled, magnetic resonance imaging study. J. Am. Coll. Cardiol. 2009; 54(19): 1787 - 1794.
10. Allen J. Taylor,Lance E. Sullenberger, Hyun J. Lee, Jeannie K. Lee, Karen A. Grace. A Double-Blind, Placebo-Controlled Study of Extended-Release Niacin on Atherosclerosis Progression in Secondary Prevention Patients Treated With Statins. Circulation. 2004;110:3512-3517.
11. Guyton JR. Extended-release niacin for modifying the lipoprotein profile. Expert Opin Pharmacother. 2004; 5: 1385–1398.
12. Bays HE, McGovern ME. Once-daily niacin extended release/lovastatin combination tablet has more favorable effects on lipoprotein particle size and subclass distribution than atorvastatin and simvastatin. Prev Cardiol. 2003; 6: 179–188.
13. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004; 110: 3512–3517.
14. F. A. Jaffer. Assessing niacin as an atherosclerosis therapeutic agent valuable insights provided by high-resolution vascular magnetic resonance imaging. J. Am. Coll. Cardiol. 2009; 54(19): 1795 - 1796.
15. Muller, H. Mehling, B. Otto, R. Bergmann-Lips, F. Luft, J. Jordan, and R. Kettritz. Niacin Lowers Serum Phosphate and Increases HDL Cholesterol in Dialysis Patients. Clin. J. Am. Soc. Nephrol. 2007; 2(6): 1249 - 1254.