

Biostatistical Analysis of Morbidity & Mortality Due to Myocardial Infarction and its Prevention by Hypolipidemic Drug Regimen

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ABSTRACT

Old age, chronic continuous smoking, alcohol intake, high blood pressure, sedentary life style, high serum lipid levels are well known risk factors for atherogenesis leading to morbidity and mortality due to myocardial infarction. The research study was planned to observe effects of Nicotinic acid (niacin) and psyllium husk on blood pressure, body weight, LDL-cholesterol, triglycerides and HDL-cholesterol. It was single blind placebo controlled research study, which was conducted at Lahore Journal Hospital, from April 2010 to December 2010. One hundred and ninety-five male and female hyperlipidemic patients were included in the research study, among which 65 were on placebo as control group, 65 were on tablet Niacin, 2.25 grams daily, in divided doses for the period of three months and 65 patients on combined drug therapy; i.e. Niacin 2.25 grams + Psyllium husk 10 grams in divided doses for the period of three months. Diabetes Mellitus, Peptic Ulcer, Renal Disease, Hepatic Disease, Hypothyroidism and Alcoholism were exclusion criteria for all participants in this research work. Body weight and blood pressure of patients were recorded at fortnightly visit. All parameters of Lipid Profile were estimated at day-0 (at start of research work) and at day-90 (at the end of the research work). 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 \pm SD and "t" test was applied to determine statistical significance of results. A probability value of <0.05 was the limit of significance. Two patients were dropped from drug-1 group of the research work due to their personal reasons. In three months of treatment with 2.25 grams of niacin HDL-cholesterol increased 16.8 %, LDL-C decreased 22.7 %, triglycerides 15.3%, systolic blood pressure 2.2 %, diastolic blood pressure 1.4%, and body weight decreased 1.9 %. With combination therapy by Niacin + Psyllium, HDL-C increased 17.5%, LDL-C decreased 25.6%, triglycerides 18.9%, systolic blood pressure 2.3%, diastolic blood pressure 3.3%, and body weight reduced 2.9%, when compared with placebo group. We concluded from the research study that niacin alone and in combination with Psyllium husk decreases blood pressure, body weight, triglycerides, LDL-Cholesterol and increases HDL-Cholesterol in primary hyperlipidemic patients, which can be a statistical significance of hypolipidemic agents to decrease risk of myocardial infarction, so the decrease in morbidity/ mortality rate due to this condition. **Key words:** Myocardial Infarction, Psyllium Husk, Nicotinic Acid, Low Density Lipoprotein Cholesterol,

INTRODUCTION

Recent research works on LIPIDS explained that atherosclerosis, if not stopped at earlier steps may lead to development of myocardial infarction. Myocardial Infarction is a common cause of morbidity and mortality throughout the world. Each 1% increase in the serum cholesterol concentration results in 2-3% increase in MI risk.¹ The levels below 200 mg/dl are classified as desirable blood cholesterol, those 200 to 239 mg/dl as borderline high blood cholesterol and those 240 mg/dl and above as high blood

cholesterol. The cut point that defines high blood cholesterol (240 mg/dl) is a value above which risk of Myocardial infarction rises steeply. The cut points recommended are uniform for adult men and women of all ages.² Dyslipidemia is diagnosed by measuring the plasma levels of total cholesterol. Routine measurements that can help to diagnose dyslipidemia include total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol measurements. The majority of cases of dyslipidemia in adults are not caused by primary disorders. They are most commonly due to secondary causes. The most common secondary cause of dyslipidemia in adults is a sedentary lifestyle coupled with excessive intake of saturated fat, cholesterol, and trans fats. Other secondary causes of dyslipidemia include diabetes

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mellitus, hypothyroidism, overuse of alcohol, and chronic kidney disease.³ Although dyslipidemia usually doesn't cause symptoms, it can lead to symptomatic vascular disease, which includes coronary artery disease (CAD) and peripheral arterial disease.⁴ Treatment of dyslipidemia is indicated for all patients who have cardiovascular disease and for some without. Treatment of dyslipidemia focuses primarily on reducing high levels of LDL cholesterol and secondarily on treating high levels of triglycerides, low levels of HDL cholesterol, and metabolic syndrome⁵. There are various drugs which decrease total cholesterol, triglycerides, LDL-Cholesterol and increase HDL-Cholesterol in primary hyperlipidemic patients, but nicotinic acid along with psyllium husk is the best LDL-Cholesterol lowering drug regimen among the lipid lowering agents. Nicotinic acid has another beneficial effect that it reduces body weight and blood pressure. Psyllium husk has more effects on cholesterol than triglycerides. When combinely administered in hyperlipidemic patients, these drugs can reduce 30% risk of developing atheroma, coronary artery disease and myocardial infarction in these patients.⁶ Nicotinic acid acts as an antilipolytic agent in adipose tissue, reducing the supply of free fatty acids and hence the availability of substrate for hepatic triglyceride synthesis and the secretion of VLDL.⁷ Psyllium husk is an oral anion-exchange resin, which binds bile acids in the intestine. Bile acids are formed from cholesterol in the liver, pass into the gut in the bile and are largely reabsorbed at the terminal leum. The total bile acid pool is only 3-5 grams but, because such enterohepatic circulation recycling takes place 5-10 times a day, on average 20-30 grams of bile acid are delivered into the intestine every 24 hours. Bile acid bound to psyllium are lost in the faeces and the depletion of the bile acid pool stimulates conversion of cholesterol to bile acid: the result is a fall in intracellular cholesterol in hepatocytes, and an increase (up-regulation) in both LDL-receptors and cholesterol synthesis. The former has the predominant influence on plasma LDL-cholesterol, which falls by 20-25%⁸.

MATERIAL & METHODS

Research was conducted at Lahore Journal Hospital Lahore and duration of study was 3 months, starting from April 2010 to December 2010. 195 patients of primary hyperlipidemia were enrolled for the research, selected from ward and OPD of Lahore Journal Hospital. Male and female primary hyperlipidemic patients of 25 to 70 years age were selected. Patients with alcohol addiction, hypothyroidism, peptic ulcer, diabetes mellitus, renal

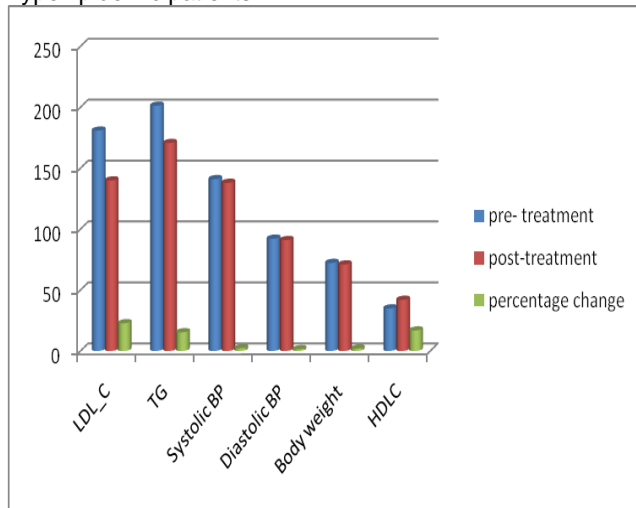
disease, hepatic disease, were excluded from the study. Written consent was obtained from all participants. Research study was started after approval by Research Ethics Committee, Lahore General Hospital, Lahore. Fortnightly follow up visit was advised to all participants. The required information like name, age, sex, occupation, address, previous medication, date of follow up visit and laboratory investigations, etc of each patient were 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 three groups, i.e. Drug-1 group, 65 patients (tab: Niacin 2.25 gm), Drug-2 group, 65 patients (Niacin 2.25 gm + Psyllium husk 10 gm) and Placebo-group, 65 patients (placebo capsules, containing equal amounts of partly grinded wheat). 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) is applied to avoid adverse effects produced by starting with higher doses of the Niacin. 65 Patients of drug-2 group were provided Tab Niacin 250 mg and 10 grams of psyllium husk to take 3 times daily in divided doses, with same advised titration of the niacin as mentioned above. For placebo group placebo capsules were given to take thrice daily in divided doses after each meal for the period of 90 days. Patients were called every 2 weeks for follow up to check blood pressure, weight, pulse rate and general appearance of the individual. Data were expressed as the mean \pm 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 respectively was used in the research. Serum LDL-cholesterol was calculated by Friedwald formula (LDL-Cholesterol=Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol).

RESULTS

Two patients discontinued to take drug Niacin due to their personal problems. So, in group-1 out of sixty five, 63 patients completed the study period that was three months. When results were summed up and test parameters were compared with placebo, it was

observed that, after three months of treatment with niacin in group-1, LDL-cholesterol decreased from 180.83 ± 1.5 mg/dl to 139.90 ± 2.2 mg/dl, which is highly significant ($P < 0.001$). The overall percentage change from day-0 to day-90 was -22.7. Niacin has increased HDL-cholesterol from 34.90 ± 1.1 to 41.99 ± 2.0 mg/dl, which is highly significant change (P -value < 0.001). In percentage it is 16.8 % increase. Triglycerides reduced from 201.22 ± 5.8 mg/dl to 170.66 ± 2.0 mg/dl, which was highly significant (P value < 0.001) reduction in three months. Systolic blood pressure reduced from 140.99 ± 3.3 mm of Hg to 137.98 ± 2.2 mm of Hg in three months, which is significant biostatistically (P -value < 0.01). Diastolic blood pressure reduced from 92.11 ± 2.0 mm of Hg to 90.98 ± 4.0 mm of Hg in this duration of treatment with 2.25 grams of Niacin. This change is not significant when compared to placebo group (P -value > 0.05). Body weight reduced from 72.22 ± 3.1 kg to 70.98 ± 1.9 kg, which is also non-significant ($P > 0.05$) when compared with placebo group.

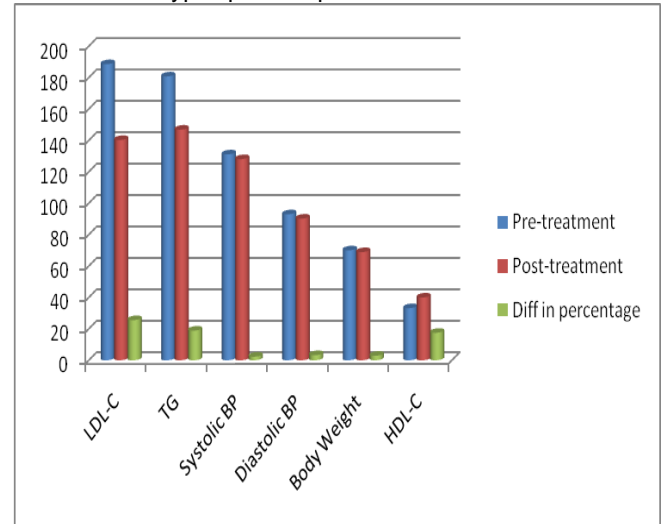
Graph 1: Effects of Niacin used for three months in 63 hyperlipidemic patients



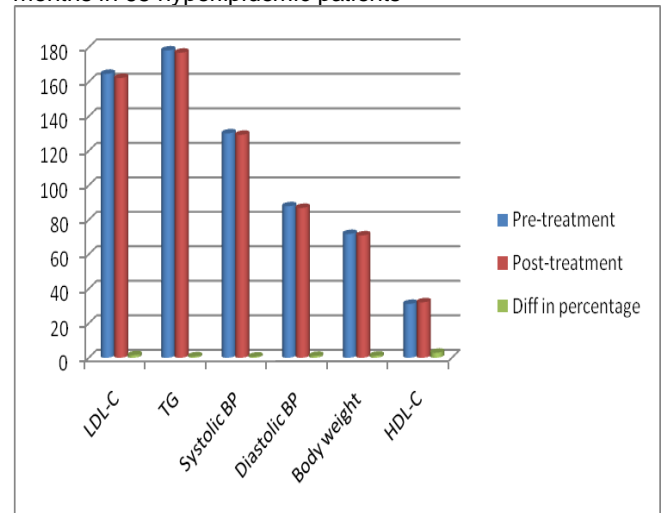
In group-2, all 65 patients completed the over all period of three months to take Niacin + Psyllium husk regularly. Their mean LDL-cholesterol at day-0 was 188.58 ± 1.7 mg/dl, which reduced to 140.29 ± 2.0 mg/dl in three months. The overall percentage decrease in the parameter was -25.6. At day-0 their mean HDL-cholesterol was 33.22 ± 1.09 mg/dl which increased to 40.01 ± 1.5 mg/dl in three months, which is highly significant statistically. At day-0 their mean triglyceride level was 180.77 ± 3.9 mg/dl which reduced to 146.88 ± 3.3 mg/dl in 90 days of treatment. It is highly significant change as compared to placebo results. At base line their mean systolic BP was 131.12 ± 2.3 mm of Hg which reduced to 128.11 ± 2.0 mm of Hg in three months. It is highly significant

difference when compared to placebo group. Diastolic BP at day-0 was 93.01 ± 2.8 mm of Hg which reduced to 90.20 ± 2.8 mm of Hg in 90 days of treatment when combined drugs were given. It is significant change statistically with P -value of < 0.01 . Mean body weight in this group was 70.01 ± 3.5 kg which reduced to 68.91 ± 4.7 kg in three months of treatment which is also significant with P -value of < 0.01 . In placebo group at day-0, LDL-cholesterol level was 164.64 ± 1.5 mg/dl, which decreased to 162.23 ± 1.9 mg/dl, which is non-significant ($P > 0.05$).

Graph 2: Effects of Niacin and Psyllium husk used for three months in 65 hyperlipidemic patients



Graph 3, Effects of Placebo capsules used for three months in 65 hyperlipidemic patients



Key: (Mean values and percentage difference of all parameters are shown here. LDL-C stands for low-density lipoproteins cholesterol, TG stands for triglycerides, BP stands for blood pressure, HDL-C stands for high-density lipoproteins cholesterol. LDL-C, HDL-C and Triglycerides are measured in mg/dl, Blood pressure is measured in mmHg & body weight is measured in Kg)

The overall percentage decrease in the parameter was -1.5. Mean HDL-cholesterol in this group at baseline was 31.22 ± 1.7 mg/dl which increased to 32.17 ± 2.1 mg/dl, which is not significant change. Mean serum Triglycerides at day-0 were 178.22 ± 1.7 mg/dl which reduced to 176.90 ± 1.1 mg/dl. Mean systolic BP at day-0 was 130.11 ± 1.8 mm of Hg which reduced to 129.29 ± 1.44 mm of Hg. Mean diastolic BP in this group at day-0 was 87.88 ± 4.5 mm of Hg and reduced to 86.91 ± 1.0 mm of Hg in three months of treatment with placebo. Mean body weight in this group was 71.77 ± 3.1 kg which reduced to 70.98 ± 2.2 kg. All changes in triglycerides, body weight, systolic BP and diastolic BP are not significant (with P-value > 0.05) when results were compared from day-0 to day-90.

DISCUSSION

In 130 hyperlipidemic patients, after 3 months of treatment with Niacin and with combined drug regimen of Niacin plus Psyllium husk, results were highly significant in LDL-C, HDL-C, and serum triglycerides. Variable statistical significance was observed in other parameters like systolic/diastolic blood pressure and body weight in these two groups. In Niacin group systolic, diastolic blood pressure and body weight were reduced significantly (P-value < 0.01). In combined group (Niacin+Psyllium) systolic blood pressure was reduced significantly (P-value < 0.01) but diastolic blood pressure and body weight reduction were non significant (P-value > 0.05) when compared with changes in 65 patients of placebo group. 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. Furthermore it is already proved that combination of Niacin plus Psyllium husk is most effective drug regimen for prevention of Myocardial Infarction due to hyperlipidemia. In our research work some parameters of lipid profile have proved different changes as compared to already researched work. In our observation, HDL-cholesterol increased from 34.90 ± 1.1 to 41.99 ± 2.0 mg/dl and LDL-Cholesterol levels decreased by 22.7% in men and women with high LDL-C levels treated with 2.25 grams of Niacin. Reduction in body weight was 1.9%. Systolic blood pressure decreased 2.2% and diastolic blood pressure reduced 1.4% in three months of treatment with same dose of niacin as used in LDL lowering and HDL upraising dose. Triglycerides reduced from 201.22 ± 5.8 to 170.66 ± 2.0 mg/dl, which was highly significant (P value < 0.001) reduction in three months.

These results match with the results of study conducted by Pearson TA et al⁹ 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 14.43% increase in HDL cholesterol. In their study LDL-C reduced 22.07%, systolic BP 1.44%, diastolic BP 2.12% and body weight 1.76%, in 90 days of treatment with three grams of niacin in 47 primary hyperlipidemic patients. Results of study conducted by A L. Gould et al¹⁰ also match with our study results. In their results LDL cholesterol reduced 21.11%, systolic blood pressure 2.00%, diastolic blood pressure 1.39% and body weight 1.01%. They observed remarkable increase in HDL cholesterol in 15 female hyperlipidemic patients when two grams of niacin was used for 4 months. It was 24.87% increase. S. A. Sorrentino et al¹¹ observed that niacin is very effective among all lipid lowering drugs, that can reduced LDL cholesterol and increase HDL cholesterol remarkably. They proved 22.90% reduction in low density lipoprotein cholesterol, 14.90% decrease in triglycerides and 16.19% 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. They did not observed effects of niacin on body weight and blood pressure.

In combination therapy by niacin plus psyllium we observed 17.5% increase in HDL-C, LDL-C decreased 25.6%, TG 18.9%, systolic blood pressure 2.3%, diastolic blood pressure 3.3%, body weight 2.9% decrease in three months of treatment in 65 patients, in three months. These results match with results of research work conducted by Izzat NN et al¹² who observed 23.87% decrease in LDL-C, 16.90% increase in HDL-C and 16.65% decrease in serum triglycerides when they used 3.5 grams of niacin and 9 grams of psyllium husk in 33 male hyperlipidemic patients for the period of 5 months. Results of research study conducted by L. Yvan-Charvet et al¹³ are in contrast with our results in combination therapy by niacin and psyllium husk, who observed only 17.45% decrease in LDL-Cholesterol in 54 hyperlipidemic patients for the period of 6 months. In their observation systolic and diastolic blood pressure reduced 1.56 and 1.21% respectively. Body weight was reduced 2.02%. These findings do not match with our results, except body weight. The reason for difference may be due to sample size and environmental factors. Their patients strictly followed step-I diet, along with taking drug. Change in sedentary life style, diet restriction along with taking hypolipidemic drugs are already proved factors of "Good and Controlled Management of Hyperlipidemia". Our results do not match with results of research work conducted by Hiatt JG et al¹⁴ who

proved 10.87% decrease in LDL-C, 12.81% increase in HDL-C, and 0.31% decrease in body weight in 10 male and female hyperlipidemic patients when 2 grams of niacin and 6 grams of psyllium husk was used for the period of 4 weeks. Obvious reasons for this difference in results are small sample size and less duration of drug used by their patients. Results of double blind placebo-controlled research study conducted by Schectman G and Hiatt J¹⁵ are also in contrast with our results who observed 11.11% increase HDL-C in 23 primary hyperlipidemic patients when treated with 4 grams of niacin and 12 grams of ispaghola (psyllium husk) for the period of 7 months in well organized 'Lipid Research Clinic'. They observed 12.99%, 10.74%, 0.98% decrease in LDL-C, triglycerides and body weight respectively. These differences in results may be guessed due to difference in study design, sample size and dose of drugs given in their patients.

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