ORIGINAL ARTICLE

Placebo controlled study on Comparison of effects of Nigella Sativa and Nicotinic Acid along with Low Fat Diet and Physical Exercise on LDL-Cholesterol and HDL-Cholesterol

HAFIZ MOEEN-UD-DIN[1], SHAH MURAD[2], AJAZ FATIMA[3]

ABSTRACT

To get good compliance of therapeutic goal of hypolipidemic agents by cardiologist and patient, some herbal drugs have had been used by some expert cardiologists. Among those herbal medicines Kalonji is most important drug used as hypolipidemic agent. In this research work hypolipidemic effects of kalonji are compared with hypolipidemic effects of Niacin. It was single blind placebo-controlled comparative study, conducted at Jinnah Hospital, Lahore from September 2013 to December 2013. Ninety hyperlipidemic patients were enrolled after written and well explained consent. Ninety patients were divided in three groups, one group as placebo and other two groups for Niacin and kalonji. After six weeks of therapy by 2 medicines, research proved highly significant changes in LDL-cholesterol, but significant changes in HDL-cholesterol in hyperlipidemic patients.

Keywords: Nigella sativa, Nicotinic acid, atherosclerosis, High and low density lipoprotein cholesterol.

INTRODUCTION

Increased concentration of low density lipoprotein (LDL) cholesterol or decreased level of high density lipoprotein (HDL) cholesterol are important risk factors for atherosclerosis. However, an independent association of triglycerides (TG) with atherosclerosis is uncertain. Large interventional studies have shown that the reduction of total cholesterol and low-density lipoprotein cholesterol (LDL-C) is one of the cornerstones in the prevention of coronary artery disease. However, in up to 40% of patients the recommended target of LDL-C is not reached with a monotherapy. Furthermore, risk stratification only by LDL-C disregards a substantial number of patients with dyslipidemia with increased triglycerides and decreased high-density lipoprotein cholesterol (HDL-C)[1-3,7]. Physical inactivity is a modifiable risk factor for cardiovascular disease and other chronic diseases, including diabetes mellitus, cancer (colon and breast), obesity, hypertension, bone and joint diseases (osteoporosis and osteoarthritis), and depression[2,4,6-8]. Little evidence of the effects of moderate-fat (from monounsaturated fat) weight-loss diets on risk factors for cardiovascular disease exists because low-fat diets are typically recommended.[4-9] Hypolipidemic effects of statins, Nicotinic acid, resins and Fibrates is well established. But herbal therapy is going to get popularity after gross root based medical

----

[1]Assistant Professor, Anatomy Department, Allama Iqbal Medical College, Lahore.
[2] Professor and HOD, Pharmacology, IM&DC, Islamabad.
[3]Assistant Professor of Pharmacology, LM&DC, Lahore.
Correspondence to Moeen-ud-din, Email: shahhmurad65@gmail.com, Cell: +92-3142243415

research in the field of medicinal plants, like Kalonji, nuts, bitter melon (Momordica charantia), Chlorophytum borivilianum root, *Sempervivum tectorum* extract, garlic, Milletia pinnata, stone apple (aegle marmelos) etc. Among lipid lowering drugs, HMG-CoA reductase inhibitors are widely used drugs for lowering so called "bad" cholesterol and increasing "good" cholesterol[2,4,9]. The hypolipidemic effect of Nigella Sativa has been demonstrated, earlier, in experimental animals. These studies reported that Nigella Sativa has a favorable effect on TG and lipoprotein pattern in normal rats.Similar findings were encountered by the administration of thymoquinone, the active ingredient of NS, to rabbits fed on cholesterol-enriched diet and to hypercholesterolemic rats[10]. Nonsignificant favorable impact of NS on serum lipids was detected in human adults and in central obese men. Recently, after many research studies, niacin has gained attention as a component of a combined therapeutic approach in patients with dyslipidemia. Niacin substantially increases HDL-C and decreases triglycerides, LDL-C and lipoprotein (a). By this mechanism of action niacin exhibited, in combination with statins or bile acid-binding resins, favorable effects on the incidence of cardiovascular events in selected patients[11].

MATERIAL & METHOD

It was single blind research conducted at Jinnah Hospital, Lahore from September 2013 to December 2013. Ninety hyperlipidemic patients were enrolled, excluding patients of renal, hepatic, thyroid disorders. Written consent was taken from all participants.

Important data like name, age, gender, occupation, residential address, phone/contact number, previous medical history, disease in family history, drug history were recorded in specific Performa. Three groups I, II, and III were made (30 patients in each group). Group-I was allocated for placebo, to take placebo capsule once daily, after breakfast for six weeks. Group-II was advised to take 2 tea spoons of kalonji after breakfast for the period of six weeks. Group-III was on Niacin 2 grams in divided doses, after breakfast, lunch and dinner for 6 weeks. Their base line LDL-cholesterol and HDL-cholesterol level was estimated at the start of research work. Their serum was taken at follow up visits, fortnightly for lipid profile. Serum LDL-cholesterol was calculated by formula (LDL-Cholesterol=Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol). Serum HDL-cholesterol was determined by using kit Cat. # 303210040 by Eli Tech Diagnostic, France. Data were expressed as the mean±SD and 't' test was applied to determine statistical difference in results. A p-value > 0.05 was considered as non-significance and P-value < 0.001 was considered as highly significant change in the differences.

RESULTS

After six weeks of treatment with KALONJI+low fat diet+40 minutes brisk walk and NIACIN+low fat diet+40 minutes brisk walk, results were summed up in mean values of LDL-cholesterol and HDL-cholesterol. Results were analyzed biostatistically. In placebo group, LDL-cholesterol decreased from 189.15±3.90 mg/dl to 186.75±2.08 mg/dl, change in the parameter is 2.40 mg/dl. This difference in pretreatment and post treatment value is non-significant, ie; P-value > 0.05. HDL-cholesterol in placebo group increased from 36.11±2.11mg/dl to 37.17±1.51mg/dl. The difference in parameter was 1.06mg/dl. Statistically this change in parameter was nonsignificant, ie; P-value > 0.05. In Nigella sativa group , out of 30 hyperlipidemic patients, 27 patients completed over all study period. LDL-cholesterol in this group decreased from 202.45±1.54mg/dl to 189.52±2.21mg/dl. The difference in pretreatment and postreatment mean values is 12.93 mg/dl. Statistically this change in two mean values is highly significant, with p-value < 0.001. HDL-cholesterol in this group increased from 38.81±3.90 42.19±3.32mg/dl. Change in two mean values was 3.38mg/dl. Statistically this change is significant, with probability value <0.01. In group III, 28 patients completed the research. LDL-cholesterol in this group decreased from 212.65±2.32 to 185.61±3.43 mg/dl in six weeks treatment. Change in pre and post treatment mean values is 27.04mg/dl. Statistically this change is highly significant, i.e., P-value < 0.001. HDL-cholesterol increased from 39.19±2.01 to 43.00±3.07 mg/dl in six weeks. Change in two parallel values is 3.49mg/dl, which is significant with P-value <0.01. Values of both parameters at baseline and after treatment with all aspects of differences and p-values are shown in following table.

Table: Showing difference in mean values of LDL-C, HDL-C, difference in mean values of drug groups as compared to Placebo group and Difference in percentage

Groups	Pre-treatment	Post-treatment	Difference in pre & post-treatment values	p-value
Placebo (n=30)	LDL-c=189.15±3.90	LDL=186.75±2.08	2.40	> 0.05
	HDL-c=36.11±2.11	HDL=37.17±1.51	1.06	> 0.05
NS (n=27)	LDL-c=202.45±1.54	LDL=189.52±2.21	12.93	< 0.001
	HDL-c=38.81±3.90	HDL=42.19±3.32	3.38	< 0.01
Niacin (n=28)	LDL-c=212.65±2.32	LDL=185.61±3.43	27.04	< 0.001
	HDL-c=39.19±2.01	HDL=43.00±3.07	3.49	< 0.01

KEY: NS stands for Nigella Sativa. Both parameters (LDL-C & HDL-C) are measured in mg/dl, n stands for sample size, LDL-c stands for low density lipoprotein cholesterol, HDL-c stands for high density lipoprotein cholesterol, p-value >0.05 indicate non-significant, <0.01 indicate significant and <0.001 indicate highly significant change in results.

DISCUSSION

In this research study drug Nigella Sativa (Kalonji) decreased LDL-cholesterol 12.93 mg/dl by six weeks of treatment. HDL-cholesterol increased 3.38 mg/dl by taking this drug for six weeks. The change in both parameters were significant. In placebo group, LDL-C reduction was 2.40 mg/dl and increase in HDL-C was 1.06 mg/dl with P-value >0.05, which proves non-significant change in results. These results match with El-Dakhakhny M[13] who did prove that Nigella sativa is very effective hypolipidemic drug. He tested the drug on 120 hyperlipidemic and diabetic patients by using Nigella sativa for one month. Their results were highly significant when compared with placebo-controlled group. Our results also match with results of Bamosa AO[14] who proved LDL-Cholesterol reduction from 201.61±3.11 mg/dl to 187.16±2.10 mg/dl in fourty hyperlipidemic patients. Their HDL-C increase was 3.98 mg/dl which also matches with our results. Results of our study are in contrast with results of research work conducted by BAMOSA and Ali BA[15] in 2002. They explained that some active

ingredients of Nigella sativa are hypolipidemic but their hypolipidemic effects are very narrow spectrum. Their results showd only 2.11 mg/dl change in LDL-C and 0.92 mg/dl increase in HDL-C of 38 rats. Difference in results may be genetic variants of human and rats. Bruckert E et al[16] also described phenomenon of genetic variation in pharmacological effects of Nigella sativa. Huda Kaatabi et al[17] have also mentioned bizzare effects of Nigella sativa with different genetic make ups. Our results also match with results of research work of Bustos C et al[18] and Nawrocki BJW et al[19]. Same mechanism of action of drug Nigella sativa is described by Gad AM et al[20]. In our research Niacin reduced LDL-Cholesterol from 212.65±1.19 mg/dl to 185.61±1.65 mg/dl in six weeks. This reduction in LDL-C was 27.04 mg/dl, which is highly significant change, when analyzed statistically. These results match with resultsn of research work conducted by Illingworth DR et al[21] who proved almost same change in LDL-C in 32 hyperlipidemic patients who were vitamized by secondary hyperlipidemia and used Niacin 2 grams daily for two months. Their LDL-C reduction was 25.55 mg/dl. Their HDL-C increase was 6.65 mg/dl in 2 months. In our results HDL-C increase was 3.81 mg/dl in six weeks use of Niacin. Our results also match with results of research conducted by Canner PL et al[22] who proved 27.77 mg/dl reduction in LDL-C in 19 hyperlipidemic patients. Chapman MJ et al[23] also support our results, as they proved 4.00 mg/dl increase in HDL-C when two grams of Niacin was used in 34 hyperlipidemic patients for six weeks. Our results do not match with results of research conducted by Brown G[24] who proved that 2.5 grams Niacin decreased 10.99 mg/dl LDL-Cholesterol. HDL-C increase was only 1.11 mg/dl. These differences may be considered due to lack of physical exercise and no restriction of use of lipids in their diet. Knopp R et al[25] used Niacin 1.5 grams in 29 hyperlipidemic patients for 3 weeks. Patients reduced their LDL-C from 189.88 ±1.11 mg/dl to 187.87±0.99 mg/dl. Difference in their results and our results is due to less sample size, lesser duration of exposure of patients to drug and small amount of drug given in their patients. Willibald et al[26] explained that Niacin lowers serum LDL-C through several mechanisms. It inhibits the peripheral mobilization of free fatty acids, which decreases the substrate available for hepatic synthesis of triglycerides and very low-density lipoprotein (VLDL) particles. This in turn reduces hepatic conversion of VLDL particles to LDL particles. In addition, niacin appears to interfere directly with the enzymatic process that mediates the conversion of VLDL-C to LDL-C and decreases triglyceride synthesis and hepatic lipoprotein secretion via inhibition of diacylglycerol acyltransferase.

REFERENCES

1. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus.JAMA.1990;264:723-726.
2. Young SG, Parthasarathy S. Why are low density lipoproteins atherogenic? West J Med. 1994;160:153-164.
3. Kruth HS. Subendothelial accumulation of unesterified cholesterol: an early event in the atherosclerotic lesion development. Atherosclerosis.1985;57:337-341.
4. Frank JS, Fogelman AM. Ultrastructure of the intima in WHHL and cholesterol-fed rabbit aortas prepared by ultra-rapid freezing and freeze-etching.J Lipid Res. 1989; 30:967-978.
5. Chun-Lai T, Padyukov L, Dhaliwal JS, Lundström E, Yahya A, Muhamad NA, Klareskog L, Alfredsson L, Larsson PT, Murad S. Shared epitope alleles remain a risk factor for anti-citrullinated proteins antibody (ACPA)--positive rheumatoid arthritis in three Asian ethnic groups. Malaysian Epidemiological Investigation of Rheumatoid Arthritis (MyEIRA) Study Group. PLoS One. 2011; 6(6):e21069. Epub 2011 Jun 15.
6. Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: current evidence and research issues.Med Sci Sports Exerc1999;31:S646-62.
7. McAuley E. Physical activity and psychosocial outcomes. In: Bouchard C, Shephard RJ, Stephens T, editors. Physical activity, fitness and health: the consensus knowledge. Champaign (IL): Human Kinetics; 1994. p. 551-68.
8. Taylor RS, Brown A, Ebrahim S et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 2004;116:682-92.
9. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? [discussion S419-20]. Med Sci Sports Exerc2001;33:S379-99.
10. Clifton PM, Bastiaans K, Keogh JB. High protein diets decrease total and abdominal fat and improve CVD risk profile in overweight and obese men and women with elevated triacylglycerol. Nutr Metab Cardiovasc Dis. 2009 Oct;19(8):548-54.
11. Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, Robinson E, Wareham NJ. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. Am J Clin Nutr. 2002 Jan;75(1):11-20.
12. Volek JS, Sharman MJ, Gómez AL, DiPasquale C, Roti M, Pumerantz A, Kraemer WJ. Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. J Am Coll Nutr. 2004 Apr; 23(2):177-84.
13. el-Dakhakhny M. Studies on the Egyptian Nigella sativa L Part-IV: Some pharmacological properties of the seeds active principle in comparison to its dihydrocompound and its polymer. Arzneimittelforschung. 1965;15:1227–9.

14. Bamosa AO. Effect of oral ingestion of Nigella sativa seeds in some blood parameters. Saudi Pharm J.1997; 5:126–9.
15. Bamosa AO, Ali BA, al-Hawsawi ZA. The effect of thymoquinone on blood lipids in rats. Indian J Physiol Pharmacol. 2002;46:195–8.
16. Bruckert E, Baccara-Dinet M, McCoy F, Chapman J. High prevalence of low HDL-cholesterol in a pan-European survey of 8545 dyslipidaemic patients. Curr Med Res Opin 2005; 21:1927–1934.
17. Huda Kaatabi, Abdullah O. Bamosa, Fatma M. Lebda, Abdulmohsen H. Al Elq, Ali I. Al-Sultan.Favourable impact of Nigella sativa seeds on lipid profile of type-2 diabetic patients. J Family Community Med. 2012 Sep-Dec; 19(3): 155–160.
19. Bustos C., Hernandez Presa, et al. Nigella Sativa reduces neointimal inflammation in a rabbit model of atherosclerosis Am. Coll.Cardiol.1998; 32:2057-2064.
20. Nawrocki JW, Weiss SR, Davidson MH, Sprecher L, Schwartz SL, Lupien PJ, et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by Nigella sativa. Arterioscler Thromb Vasc Biol 1995; 15:678-82.
21. Gad AM, El-Dakhakhany M, Hassan MM. Studies on the chemical constitution of Egyptian Nigella sativa L oil. Planta Med. 1963;11:134–8.
22. Illingworth DR, Stein EA, Mitchel YB et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. Arch Intern Med. 1994;154:1586-1595.
23. Canner PL, Berge KG, Wenger NK et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol.1986;8:1245-1255.
24. Chapman MJ, Assmann G, Fruchart JC, Shepherd J, Sirtori C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid–a position paper developed by the European Consensus Panel on HDL-C. Curr Med Res Opin 2004;20:1253–1268.
25. Brown G. Maximizing coronary disease risk reduction using nicotinic acid combined with LDL-lowering therapy. Eur Heart J 2005;7:Suppl., F34–F40.
26. Knopp R, Ginsberg J, Albers JJ et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism. 1985; 34: 642-650.
27. Willibald Hochholzer, David DG, Robert PG. The Facts Behind NiacinTher Adv Cardiovasc Dis. 2011;5(5):227-40.