ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

COMARATIVE EFFECT OF LOW DOSE BETWEEN AMLODIPINE AND NIFEDIPINE ON SERUM CHOLESTEROL PROFILE OF RABBITS RECEIVING HYPERLIPIDEMIC DIET.(VANASPATI GHEE)

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Manuscript Info

Manuscript History:

Received: 13 July 2013
Final Accepted: 19 July 2013
Published Online: August 2013

Key words:
Hyperlipidemic diet–standard diet-Amlodipine v/s, Nifedipine - serum cholesterol profile

Abstract

Objective: To know &compare the effect of low dose amlodipine v/s nifedipine on serum cholesterol profile of rabbits receiving hyperlipidemic diet.

Methods & Materials: The plan consists of selection of seventy Newzealand rabbits for the study. Seven groups of rabbits were made . Each group consists of 10 rabbits. The serum cholesterol profile was estimated at the beginning before starting the drug administration and then after ten weeks of the drug administration of each rabbit of all group. For analysis of cholesterol profile i.e. total cholesterol, HDL-cholesterol and LDL-cholesterol 1ml blood samples were collected from the marginal ear vein of rabbit after an overnight fast.

Results: There was very highly significant increase in the total cholesterol in the treatment groups V & VI as compared to all pretreatment groups & treatment group VII at the end of 10 week .While there was decreased rise in total cholesterol significantly in group VII as compared to group V after 10 week treatment. Total cholesterol in the group –IV receiving amlodipine group decreased from 97±4.06 mg/dl to 90±4.2 mg/dl& HDL-Cholesterol increased from 32.01±4.40 mg/dl to 37±4.60 mg/dl after 10 week treatment but these changes were not significant. While LDL cholesterol was decreased significantly in rabbits with low dose of amlodipine in group IV with 10 week treatment from 55.42±3.32 mg/dl to 32.40±3.22 mg/dl . In the group - III receiving nifedipine there was a non significant increase in total cholesterol from 102.49±5.16 mg/dl to 106±5.39 mg/dl, HDL cholesterol from 34.10±2.80 to 35.16±2.82 mg/dl and LDL cholesterol from 56.20±2.20 mg/dl to 59.00±2.20 mg/dl after 10 week treatment. The HDL-cholesterol was increased in post-treatment groups IV &VII as compared to all pretreatment groups & treatment groups V&VI marginally. While HDL-c was marginally decreased in post-treatment groups V&VI. There was marked rise in LDL-C in group-V from **58.52±2.40 to 258.89±2.40 & Gr-VI from 50.12 ± 3.99 to 231.91 ± 3.99** as compared to all pretreatment groups & test groups I, II & III after 10 week treatment .While there was significant decreased rise of LDL-C in treatment group-VII as compared to treatment group-V at the end of 10weeks

Conclusion: The study shows amlodipine produces favorable alterations in serum cholesterol profile as compared to Nifedipine in rabbits fed on hyperlipidemic diet.

Introduction

The coronary artery disease consists of two components i.e. Hyperlipidemia and hypertension. The coronary artery disease is precepited by high serum levels of total cholesterol and low density lipoprotein cholesterol. The National cholesterol education program (NCEP 1988) reported& focused attention on the necessity for managing lipid disorders[17].The abnormal levels of total cholesterol and low -density lipoprotein cholesterol play a major role in the atherosclerotic process. While the high density lipoprotein particles function in the opposite way from low density lipoprotein, they act as a scavenger of free cholesterol and enhance the rate of clearance of cholesterol from the arteries[4]. There are various reports regarding animal and human experimental studies that various classes of antihypertensive agents have either adverse or significant, effect on plasma lipid & lipoprotein levels [1,5,6]. The beta-blockers without partial intrinsic sympathomimetic activity increase serum triglycerides and tend to lower high-density lipoproteincholesterol[13]. Recently there has been an epidemical increase in hypertensive cases resulting into coronary artery disease due to abnormal lipid profile. Therefore we planned in this study to see whether amlodipine versus nifedipine to test if this drug having antihypertensive effect in human, has any effect on serum cholesterol profile of rabbits fed on hyperlipidemic diet. In this study hyperlipidemic diet utilized was vanaspati toop/ghee i.e. solid state condensed oil derived plant source-sunflower .

MATERIALS AND METHOD

Seventy healthy male Newzealand rabbits weighing between 2-3 Kg were selected. They were placed under ideal conditions. Animals were maintained on routine feed and acclimatized for seven days prior to start of the experiment. Nifedipine (Pfizer Ltd): A solution of 5 mg/40ml in propylene glycol prepared and administered orally in a dose of 2ml/kg i.e. 0.25 mg/kg orally. Amlodipine (Pfizer Ltd):A solution of 2.5mg/40 ml in propylene glycol prepared and administered orally in a dose of 2ml/kg i.e. 0.125 mg/kg orally. Estimations of serum total cholesterol and serum high and low density lipoprotein cholesterol were done at the beginning of the study and after 10 weeks of administration of the study drug

STUDY DESIGN

The rabbits were divided into seven groups containing 10 rabbits each. A routine diet containing bread, milk and vegetable on an average of 100gm/rabbit was given to the rabbits during the study period with water given ad-libitum. The groups before treatment were as follows:

Group I: Routine diet (control group)

Group II: Routine diet with-out vehicle propylene glycol 2ml/day

Group III: Routine diet + & with-out Nifedipine (0.25mg/kg/day)

Group IV: Routine diet &with-out Amlodipine 0.125mg/kg/day orally

Group V: Rabbits fed on only with routine diet & with-out vanaspati toop/ghee 5gm/kg .

Group VI: Rabbits fed only on routine diet but without vanaspati toop/ghee 5gm/kg & Nifedipine 0.5mg/kg

Group VII: Rabbits fed only on routine diet but with-out vanaspati toop/ghee 5gm/& Amlodipine 0.25mg/kg.

Table: 1.Cholesterol profile in the pretreatment/basal group of rabbits.(n=10)

Serial. No	Group	Total Cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
	Group I	95.00± 1.28	32.16± 2.08	56.55±3.72
	Group II	97.00± 1.28	34.01± 3.20	54.20± 5.20
	Group III	102.49± 5.16	34.10± 2.80	56.20± 2.20
	Group IV	97.00± 4.06	32.01± 4.40	55.42± 3.32*
	Group V	96.oo± 4.51	38..12±3.37	58.52±2.40
	Group VI	102.5± 9.5	37.00±4.56	50.12±3.99
	Group VII	96.40±3.19	33.35 ±2.76	54.12±2.98

THE RABBITS AFTER TREATMENT:

The rabbits were divided into seven groups containing 10 rabbits each. A routine diet containing bread, milk and vegetable on an average of 100gm/rabbit was mixed with vanaspati toop/ghee given to the rabbits during the study period with water given ad-libitum to respective groups. The groups after treatment were as follows:

Group I: Routine diet (control group)

Group II: Routine diet +vehicle propylene glycol 2ml/day

Group III: Routine diet + Nifedipine (0.25mg/kg/day) in a vehicle propylene glycol 2ml/day orally

Group IV: Routine diet + Amlodipine 0.125 mg/kg /day in a vehicle propylene glycol 2ml /day orally

Group V : Rabbits fed on routine diet + vanaspati toop/ghee 5gm/kg along-with vehicle 2ml/day.

Group VI: Rabbits fed on routine diet + vanaspati toop/ghee 5gm/kg +Nifedipine 0.5mg kg in a vehicle propylene glycol 2ml/day orally

Group VII: Rabbits fed on routine diet + vanaspati toop/ghee 5gm/+ Amlodipine 0.25mg/kg in a vehicle propylene glycol 2ml/day orally.

The animals were treated in this manner for 10 weeks. For analysis of cholesterol profile i.e. total cholesterol, HDL-cholesterol and LDL-cholesterol 1ml blood samples were collected from the marginal ear vein of rabbit after an overnight fast after ten weeks of the drug administration with hyperlipidemic diet. Readings were taken on a photo colorimeter. The data were analyzed using students paired‘t’ test for the same group & students unpaired ‘t’ test between the group.

Table: 2. Cholesterol profile after 10 weeks treatment groups of rabbits.(n=10)

Serial. No	Group	Total Cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
	Group I	99.00± 1.28	31.02± 2.08	53.12± 3.72
	Group II	100.00± 1.28	34.00± 3.20	55.00± 5.20
	Group III	106.00± 5.19	35.16± 2.82	59.00± 2.20
	Group IV	90.00± 4.06	37.00± 4.60##	32.40± 3.32*
	Group V	193.0± 4.51**	34.12-± 3.34	258.89± 2.40
	Group VI	153.00± 5.66**	35.00± 4.56	231.91± 3.99
	Group VII	108.00± 3.19	37.00± 2.76##	79± 2.98#

1)The data were analyzed by using students paired ‘t’ test for the same group &students unpaired ‘t’ test between the groups

2) * = in comparison with group I & # = in comparison with group V&VI>
* & # = p<0.001 (highly statistically significant)

3) ** = in comparison with VII, ** = p<0.01 , (statistically significant)

4) ## = in comparison with group III V&VI , ## = p<0.05, (not statistically significant)

RESULTS

The difference in the total cholesterol at the beginning of the study & at the end of 10 week treatment is not significantly altered in groups I,II,III & IV. There was very highly significant increase in the total cholesterol in the treatment groups V &VI as compared to all pretreatment groups & treatment group VII at the end of 10 week (p<0.01).While there was decreased rise in total cholesterol significantly in group VII as compared to group V after 10 week treatment. There is also slight decrease in total cholesterol in group IV in treatment group as compared to pretreatment groups I,II&III. The HDL-cholesterol was altered in post-treatment groups IV&VII as compared to all pretreatment groups

&treatment groups III ,V &VI marginally. ($p>0.05$).While HDL-c was marginally decreased in post-treatment groups V&VI. There was marked rise in LDL-cholesterol in treatment group V&VI as compared to the all pretreatment groups & treatment group I, II &, III. While there was decreased rise in LDL-cholesterol significantly in group VII as compared to treatment groups V&VI ($p<0.001$). There was also non- significant reduction in LDL-C in group IV receiving amlodipine as compared to group I,II,III at the end of 10week treatment. Thus amlodipine has prevented considerable rise in total &LDL-C significantly in treatment group VII rabbits. This indicates superiority of amlodipine over nifedipine as far as serum cholesterol profile in as antihypertensive agents.

DISCUSSION

The coronary artery disease consists of two components i.e. hyperlipidemia and hypertension. The coronary artery disease is precipitated by high serum levels of total cholesterol and low density lipoprotein cholesterol . Administration of only amlodipine in group IV & in group VII receiving amlodipine + hyperlipidemic diet resulted in significant lowering of LDL-C after 10 weeks when compared to group III receiving nifedipine & group V receiving hyperlipidemic diet respectively. Dr .K .L. Chopra suggested in June 1997 that a programme on prevention of coronary artery disease cannot be really successful without lowering total & LDL cholesterol . Similar effects of nicardipine in lowering LDL-C and elevating HDL-C has been reported by Ohata et al in 1984[18]. The need for an antihypertensive having favorable effect on lipid profile is felt more than ever. In this study the two dihydropyridine calcium channel blockers, nifedipine and amlodipine are investigated towards this objective. The lipids are dietary substances, esters of fatty acids ,yields 9kcal/ gm energy & present in the body as lipoprotein i.e.lipid+protein. Chemically lipids contain triglyceride ,cholesterol ester, free cholesterol & phospholipids .Dietary cholesterol also regulates endogenous hepatic cholesterol synthesis. .In the hypertension there are shearing forces causes chronic/repeated- cell injury . It is also possible that because of small size of LDL-C enters arterial wall during endothelial injury in hypertension –causes dysfunction of endothelium .This events increases permeability of monocytes & platelets – which finally through number of reactions form a plaque-result into atherosclerosis.[9&20]

Hoise J Bremner A.D.in 1992 &Webster J. &et al in1988 showed that the convenience of once daily dosing of amlodipine has clinical advantage over nifedipine retard in treatment of hypertension[12 &25].

Epidemiological studies such as the Framingham study have demonstrated an association of increased total & that too LDL-C with increased risk of atherosclerotic events along with other risk factors include diabetes hypertension& smoking [14].The effect of nifedipine and amlodipine on lipid profile of rabbits fed on hyperlipidemic diet was investigated over ten weeks. The serum total cholesterol increased within two weeks in the groups fed on hyperlipidemic diet and also in the group- that received nifedipine along with the hyperlipidemic diet. Co-administration of amlodipine delayed this rise for up to 4 weeks. In subsequent investigations at 6.8 and 10 weeks nifedipine and amlodipine prevented the rise in total cholesterol along with hyperlipidemic diet, however the effect was found to be more significant with amlodipine than with nifedipine.

Similarly amlodipine was more effective than nifedipine in preventing the rise in LDL cholesterol along with hyperlipidemic diet.

HDL cholesterol was found to be unaltered by any treatment. Nifedipine parse does not alter the favorable cholesterol profile except a non significant rise produced by nifedipine in the levels of total cholesterol and significant rise in LDL cholesterol at the end of 10 weeks.

Thus amlodipine was favorably found to be more effective than nifedipine in this respect.

The treatment of hypertension is found with potential difficulties, including the altered efficiency of medications, the increased risk of side effects and possibility for derangement of serum lipid levels. Thus serum cholesterol plays a central role in the atherosclerotic process, in particular, abnormal levels of total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol have been found to be predictors of coronary heart disease risk in hypertension. As the major transport vehicles for cholesterol, low-density lipoprotein particles essentially deposit cholesterol in the lining of the arterial wall; low-density lipoprotein cholesterol is often referred to as bad cholesterol. High-density lipoprotein particles function in the opposite way from low-density lipoprotein. They act as a scavenger of free cholesterol and enhance the rate of clearance of cholesterol from the arteries. Serum high-density lipoprotein cholesterol levels and subsequent development of coronary artery disease in hypertension were also found to be related, but in hypertension through the effects of diet on plasma lipids[22&8]. In the Framingham study ,serum HDL-C levels &subsequent development of coronary artery disease in hypertension were also found to be related in inverse proportion .[2]

Alpha blockers &alpha 2 stimulants decrease total cholesterol & triglycerides [21] . Angiotensin converting-inhibitors do not affect lipoprotein metabolism adversely[15].

Dietary factors and clinical events of coronary artery disease are linked together with hypertension through the effects of diet on plasma lipids[22&8] . For these reasons, high density lipoprotein cholesterol is often referred to as good cholesterol. Henry P.D in 1990 showed that calcium channel blockers like nifedipine and nicardipine reduce atherosclerotic lesions in cholesterol fed rabbits without any significant effect on serum lipids[10] . It has been reported that calcium channel blockers including nifedipine do not adversely affect lipid profile[11] . Trupti Rekha Swain, M Das in 1996 Showed the beneficial effect of low dose felodipine on serum cholesterol of rabbits fed on atherogenic diet[23]. The cholesterol reducing effect of felodipine, when administered early has not been explained satisfactorily. Increased uptake and degradation of low density lipoprotein by skin fibroblasts, aortic endothelial cells, smooth muscle cell, induction of denovo synthesis of apoproteins and inhibition of cholesterol synthesis and reduction of cholesterol ester accumulation in smooth muscle cells are thought to be the possible mechanisms. Many studies have demonstrated that arterial compliance is improved by antihypertensive drugs that induce vasodilatation in the large peripheral arteries, e.g. calcium antagonists, angiotension converting enzyme inhibitors and certain beta adrenoreceptor blockers. Amlodipine increased arterial compliance and dilated the brachial artery at prevailing and isobaric pressure. The active increase in arterial compliance with amlodipine was 26% of pretreatment values, while passive pressure dependent was only 14% [16]. It has been shown experimentally that a reduced response of the arterial smooth muscle to endothelial vasodilators and an increased sensitivity to vasoconstrictor agents may be involved in the abnormal arterial reactivity seem in hypercholesterolemia. The presence of calcium and its role in plaque formation is not yet fully elucidated [7]. Over the past decade, investigators have demonstrated that CCB like agents may retard plaque formation. Recent studies in patients with coronary artery disease have demonstrated that nifedipine may impede or prevent the development of atherosclerosis plaques in humans as well[24]

CONCLUSION

The present study shows that amlodipine plays a favorable role in the alteration of serum cholesterol profile. Further studies confirming these findings may open up new avenues for this novel group of drugs and pave way for their use in many appropriate situations for prevention of hypercholesterolemia.

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