Academic Sciences Asian Journal of Pharmaceutical and Clinical Research
Vol 6, Issue 1, 2013 ISSN - 0974-2441

Research Article

INDIGENOUS HERBAL PRODUCT NIGELLA SATIVA PROVED EFFECTIVE AS AN ANTIHYPERTENSIVE IN METABOLIC SYNDROME

AHMAD NAJMI[1], MOHAMMAD NASIRUDDIN[2], RAHAT ALI KHAN[3], SHAHZAD F HAQUE[4]

[1]Department of Pharmacology, Index Medical College, Indore ,[2]Department of Pharmacology, JN Medical College, AMU, Aligarh ,[3]Department of Pharmacology, JN Medical College, AMU, Aligarh,[4]Department of Medicine, JN Medical College, AMU, Aligarh ,
Email: najmi.alig@gmail.com

Received: 3 October 2012, Revised and Accepted: 1 November 2012

ABSTRACT

This study evaluated the effects of Nigella sativa (NS) on the systolic and diastolic blood pressure in patients of metabolic syndrome. We conducted an open lebeled study to test the efficacy of Nigella sativa as an antihypertensive in patients of metabolic syndrome. Patients were randomly divided into two groups (n=45 each). In group I (Std), patients were advised amlodipine 5 mg once a day, atenolol 50 mg once a day and atorvastatin 10 mg once a day for a period of eight weeks. In group II (NS group) patients were advised recommended doses of Nigella sativa (NS) in addition to abovementioned drugs for a period of eight weeks. Aspirin 150 mg was given in both groups. Each subject's BP was measured at the beginning of the study, then once every two weeks during the study. Measurements were always made at the same place and time after 15 min of rest. Venous blood was also collected from each subject before and after the study.NS significantly lowered SBP, DBP and LDL-c after 8 weeks. The NS group showed significant improvement with reference to SBP, DBP & LDL-cholesterol (P value < 0.05). Nigella sativa oil was found to be effective antihypertensive agent in patients of metabolic syndrome. The various mechanisms that may be responsible for antihypertensive effect of Nigella sativa are centrally acting antihypertensive activity, calcium channel blocking activity and its diuretic activity.

Keywords: Antihypertensive, Nigella sativa, Blood pressure

INTRODUCTION

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) that is deserving of more clinical attention. The etiology, prevention and treatment of the metabolic syndrome are currently the focus of intense research activities. A number of risk factors are associated with cerebrovascular accidents, including age, gender, elevated cholesterol, smoking, alcohol consumption, excessive weight, race, family history and hypertension[1] Although some of these risk factors cannot be modified, the controllable factor that has the greatest impact on the etiology of stroke is high blood pressure[2] The endogenous molecule nitric oxide (NO), which is released by endothelial cells through NO synthesis, is a major factor in blood vessel relaxation which may result in lowering blood pressure[3] . Since BP is kept up by several interrelated factors, an attempt to block one of them tends to increase compensatory activity of the others. It is rational in such cases to combine drugs with different mechanism of actions for example drugs which increase plasma rennin activity – diuretics, calcium channel blockers, Angiotensin converting enzyme inhibitors may be combined with drugs which lower plasma rennin activity – beta blockers, clonidine, methyldopa. The various mechanisms that were proposed for antihypertensive effect of Nigella sativa were centrally acting antihypertensive agent[4] , calcium channel blocking activity[5] and its diuretic activity[6]. Alternative medicine has opened new door for the treatment of cardiometabolic disorders which has attained epidemic proportion throughout the world. Nigella (Kalonji) (Nigella sativa) belonging to the buttercup family Ranunculaceae, is commonly known as black seeds. Nigella seeds have many pharmaceutical uses. The seeds have occupied special place for their medicinal value for centuries in the Middle East and Southeast Asia[7]. Nigella sativa seed, used for centuries for medicinal and culinary purposes and reported to possess a number of pharmacological properties, including antioxidant[8], anti-inflammatory[9], hypoglycemic[10], antihypertensive[11] and antihyperlipidemic properties[12]. Our aim is to study the effect of Nigella sativa on the blood pressure in patients of metabolic syndrome

MATERIAL & METHODS

The present study was conducted on newly detected patients of metabolic syndrome in a teaching Hospital of North India from October 2005 to March 2007.The study group comprised of 90 patients of metabolic syndrome with coexistent hypertension. . There were 52 males and 38 females. The age group of the patients varied from 20 years to 70 years but majority of the patients were in 40-60 years age group. After final diagnosis and considering inclusion and exclusion criteria patients were enrolled in this prospective study. Approval from institutional ethical committee was taken. The participants were informed of all possible expected benefits and possible harm ensuing from the study. Written consent was obtained from the study subjects. This was an open label randomized controlled study. These patients were diagnosed as having metabolic syndrome according to ATP III criteria. The exclusion criteria were pregnancy, type I diabetes mellitus, acute coronary syndromes and cerebrovascular accidents, impaired liver function test, Patients of chronic renal disease, familial dyslipidemia. Patients were randomly divided into two groups (n=45 each). In group I (Std group), patients were advised standard regimen (amlodipine 5 mg once a day + atenolol 50 mg once a day + atorvastatin 10 mg once a day) for a period of eight weeks. In group II (NSO group) patients were advised standard regimen and 500 mg capsule of Nigella sativa as add on therapy. Aspirin 150 mg once a day was given in both groups.

N. sativa seeds of indigenous variety were obtained from a local herbal market Aligarh. *N. sativa* seeds were authenticated. Then the seeds were washed, dried and crushed to a powder with an electric microniser. Five hundred milli gram capsules were made by this powder. After collecting base line data of blood pressure and lipid profile, a dose of two month Nigella sativa capsules (60 capsules) was given to patients in group II and were asked to use capsules regularly

Each subject's BP was measured at the beginning of the trial, then once every two weeks during the trial. Their BP was measured using a digital BP analyzer (ES-P110, Terumo Corp., Tokyo, Japan) and recorded as the average of two measurements. Measurements were always made at the same place and time after 15 min of rest. Venous blood was also collected from each subject before and after the trial. Blood samples were assayed for serum lipid profiles. Advices about dietary and lifestyle changes were given to both Nigella sativa and standard groups.Nigella

STATISTICAL ANALYSIS

Pre and post intervention mean ± standard deviation of each parameter was calculated for both groups. Paired t test was applied to know the intragroup difference of each variable before and after intervention. Then unpaired t test was applied to know about

intergroup difference between both groups All the statistic were done by using 13 th version of SPSS software.

RESULTS

Reduction of both systolic and diastolic blood pressure was statistically significant (P value < 0.001) after intervention in both groups. Intergroup reduction in both systolic and diastolic blood pressure was more in NS group (P value < 0.001). Reduction in both intragroup and intergroup reduction in TG was statistically more (P value < 0.001) in Std group as compared to NS group. Both intragroup and intergroup reduction in LDL was statistically more (P value < 0.001) in NS group.HDL was increased in both group but neither intragroup nor intergroup difference was significant (P value 0.122). No major adverse effects were reported by participants during the study.

Table 1: Variables Of Blood Pressure And Lipid Metabolism At baseline and after the intervention period* in both groups

Parameters	Before Intervention (Mean ± SD)	After intervention (Mean ± SD)
SBP (Std)†	172.9756 ± 10.6014	140.6076 ± 8.7941
SBP (NS)†	166.7848 ± 11.8651	130.8537 ± 9.5882
DBP (Std) †	88.6341 ± 11.4218	84.7317 ± 3.3149
DBP (NS)†	88.0253 ± 5.4055	80.848 ± 4.7167
TG (Std)†	233.5244 ± 12.7060	155.0122 ± 11.9724
TG(NS)	195.7595 ± 15.8881	180.3924 ± 12.9172
LDL (Std)	139.2805 ± 11.6439	128.2405 ± 12.5820
LDL (NS)†	163.6835 ± 12.2154	117.8780 ± 10.4107
HDL (Std)	43.1463 ± 5.4209	45.6829 ± 3.9378
HDL (NS)	44.0127 ± 4.2892	47.6203 ± 2.4456

Data are mean ± SD
†Significantly different from baseline (*P* < 0·001).

Table 2:Post treatment mean ± sd of standard (group i) and nigella sativa group (group ii)

Parameter	Post treatment Mean ± SD of Std Group	Post treatment Mean ± SD of NS group
SBP‡	140.6076 ± 8.7941	130.8537 ± 9.5882
DBP‡	84.7317 ± 3.3149	80.848 ± 4.7167
TG‡	155.0122 ± 11.9724	180.3924 ± 12.9172
HDL	45.6829 ± 3.9378	47.6203 ± 2.4456
LDL‡	128.2405 ± 12.5820	117.8780± 10.4107

Data are mean ± SD.
‡ Significantly different from the standard group (P value < 0.001)

DISCUSSION

Reduction in both systolic and diastolic blood pressure was significantly more (P value < 0.001) in Nigella sativa group as compared to standard group. Although intragroup reduction was also significant (P value < 0.001) in both groups after intervention. This indicates the synergistic effect of Nigella sativa in lowering blood pressure with other conventional drugs. The various mechanisms that were proposed for antihypertensive effect of Nigella sativa were centrally acting antihypertensive agent[4] , calcium channel blocking activity[5] and its diuretic activity[6].

Atenolol is cardioselective beta one antagonist. Because of longer duration of action once daily dose is often sufficient. Side effects related to central nervous system action are less likely. No deleterious effect on lipid profile has been noted. Amlodipine is calcium channel blocker of dihydropyridine (DHP) group. It has complete but slow oral absorption. The early vasodilator side effects like palpitation, flushing, and postural dizziness are largely avoided. Diurnal fluctuation in blood level is small and actions extend over the next morning. Its bioavailability is higher and more consistent

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provides guidelines for intensive treatment of hypertension. Although use of thiazide diuretics and beta-blockers has been avoided in patients with glucose tolerance abnormalities, the safety and efficacy of such medications have been demonstrated in large clinical trials[10] . Drugs of these classes can be used in treatment of hypertension in patients with metabolic syndrome. We had taken a combination of atenolol and amlodipine because of certain advantages. Although Joint National Committee six (JNC VII) emphasize on single drug therapy, in practice a large majority of hypertensive ultimately require two or more drugs. In the Hypertension Optimal Treatment (HOT) study, a multicenter trial conducted in 26 countries, 70 % patients who achieved target blood pressure (BP) were being treated with two drugs. Even initial treatment of mild to moderate hypertension with a low dose combination is being advocated as an alternative strategy. Since BP is kept up by several interrelated factors, an attempt to block one of them tends to increase compensatory activity of the others. It is rational in such cases to combine drugs with different mechanism of actions for example drugs which increase plasma rennin activity – diuretics, calcium channel blockers, Angiotensin converting enzyme inhibitors may be combined with drugs which lower plasma rennin activity – beta blockers, clonidine, methyldopa.

El Tahir KE et al[8] studied the effects of the volatile oil of NS seed on the arterial blood pressure and heart of urethane-anaesthetized rats and the effects were compared with those of thymoquinone.Intravenous (I.V.) administration of volatile oil (V.O.) to rats decreased arterial BP and Heart rate in a dose dependent manner. The effects of V.O. were significantly antagonized by treatment of the animals with cyproheptadine, hexamethonium, and atropine and by spinal pitting. Treatment of the animals with reserpine significantly antagonized the cardiovascular depressant effects induced by 4 and 8 µl/Kg of V.O. but not those induced by the larger doses. Thymoquinone induced cardiovascular depressant effects were significantly antagonized by atropine and cyproheptadine but not by reserpine. The results suggested that the V.O. induced cardiovascular depressant effects were mediated mainly centrally via indirect and direct mechanisms that involved 5-hydroxytryptaminergic and muscarinic mechanisms. The direct mechanisms may be due to the presence of Thymoquinone in the V.O. The V.O. seemed to possess the potential of being a potent centrally acting antihypertensive agent. This oil also inhibited the contraction of rabbit aortic rings induced by nor epinephrine stimulation[11] . An oral dose of dichloromethane extract of N. sativa increased significantly the diuresis after 15days of treatment. Simultaneously the mean arterial pressure decreased by 22%. Studies on rabbit and guinea pig tracheal smooth muscle and on isolated rabbit jejunum have suggested Ca++ channel blocking activity of N. sativa[14]

In our study we advised low dose aspirin to the patients of both standard and Nigella sativa group. People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. These abnormalities, however, are not routinely detected in clinical practice. A prothrombotic state, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected. The methanol soluble portion of black cumin oil showed inhibitory effects on Arachidonic acid induced platelet aggregation and blood coagulation. The methanol soluble part was further purified to isolate 2-(2-methoxypropyl)-5-methyl-1, 4-benzenediol, thymol and carvacrol, all having strong inhibitory activity. These isolated compounds and related compounds were examined by the screening test for Arachidonic acid induced platelet aggregation and it was found that the compounds possessing aromatic hydroxyl and acetoxyl group had more potent activity than aspirin[15]. An alternative approach to the prothrombotic state is antiplatelet therapy. For example, low-dose aspirin reduces CVD events in both secondary and primary prevention. Thus, use of aspirin for primary prevention in patients with metabolic syndrome is promising. According to current recommendations, low-dose aspirin therapy has a favorable efficacy/side effect ratio when 10-year risk for CHD is 10%.For primary prevention, the only available

long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established atherosclerotic cardiovascular disease (ASCVD) provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is an attractive therapeutic option to lower vascular events[15]

Reduction in LDL cholesterol was more in Nigella sativa group (NS) as compared to standard group. Our results were the same as reported previously in various studies. Previous research workers[16] also reported the cholesterol lowering effect of Nigella sativa oil in animal studies. The presence of various unsaturated fatty acids like Arachidonic, eicosadienoic, linoleic, linolenic, oleic and almitoleic acid[17] may be responsible for the improvement of lipid profile. The various mechanisms were proposed for the lowering of cholesterol. The seeds may either inhibit de novo cholesterol synthesis or stimulate bile acid excretion. It is well-known that both effects would lead to a decrease in serum cholesterol[18] . Further research is necessary to identify the mode of action of black cumin seeds. Increase in High density lipoprotein (HDL) was more in Nigella sativa group as compared to standard group. This difference was not significant (P value < 0.05). The same result was also reported[16] previously in rats. Reduction in Low density lipoprotein (LDL) cholesterol was significantly more (P value < 0.05) in Nigella sativa group as compared to standard group. LDL-c level may be decreased by increasing the production of LDL-c receptors[19] . Improvement in triglyceride (TG) was more in standard group as compared to Nigella sativa group. The same results were reported previously[20] . Treatment of the dyslipidemia of metabolic syndrome should involve nonpharmacologic interventions, including weight loss, exercise, and a low-fat diet. Reducing LDL-C levels with use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") is also appropriate for patients with metabolic syndrome. The ATP III guidelines recommend that LDL-C be the primary target of lipid-lowering therapy when a patient's triglyceride level is below 500 mg/dL. We had take atorvastatin because of certain advantages .Statins are competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG Co A) reductase, which catalyzes an early , rate limiting step in cholesterol biosynthesis. The statins are the most effective and best tolerated agents for treating dyslipidemia[21] Statins have certain other cardioprotective benefits besides LDL lowering like improvement in endothelial function[22] plaque stabilization[23] decreased the risk of coronary heart disease and levels of C- reactive proteins[24] inhibiting lipoprotein oxidation both in vivo and ex vivo reduce platelet aggregation[25] . Atorvastatin as a single agent may obviate the need for multiple drug therapy in high-risk patients[26]. Atorvastatin is relatively more potent, cost effective and got the highest LDL cholesterol lowering efficacy at maximal daily dose of 80 mg.Hepatic cholesterol synthesis is maximal between midnight and 2:00 A.M. Thus statins with half life of 4 hours or less (all but atorvastatin and rosuvastatin) should be taken in the evening or bed time. Atorvastatin has a long half life (18-24 hours), which allows administration of this statin at any time of the day.

CONCLUSION

Nigella sativa can be used as add on drug therapy in patients of metabolic syndrome with elevated blood pressure. Nigella sativa oil has significant activity in hypertensive & dyslipidemic patients. The various mechanisms that may be responsible for antihypertensive effect of Nigella sativa are centrally acting antihypertensive activity, calcium channel blocking activity and its diuretic activity. The various components of Nigella sativa that may be responsible for its beneficial effects in metabolic syndrome are thymoquinone, thymol, various unsaturated fatty acids, lipase and tannins.

ACKNOWLEDGEMENT

We are thankful to laboratory & OPD staff of department of pharmacology & medicine of JN Medical College, AMU, and Aligarh

REFERENCES

1. Mark, K.S. and T.P. Davis. 2000. Stroke: development, prevention and treatment with peptidase inhibitors. Peptides **21:** 1965-1973
2. Dunbabin, D. 1992. Cost-effective intervention in stroke. Pharmacoeconomics**2:** 468-499
3. Chalupsky, K., I. Lobysheva, F. Nepveu, I. Gadea, P. Beranova, G. Entlicher, J.C. Stoclet, and B. Muller. 2004. Relaxant effect of oxime derivatives in isolated rat aorta: role of nitric oxide (NO) formation in smooth muscle. Biochem. Pharmacol.**67:** 1203-1214.
4. El, Tahir. K. E. H., M. M. S. Ashour, et al. (1993). The cardiovascular actions of the volatile oil of the Black Seed (Nigella sativa) in rats: Elucidation of the mechanism of action
5. Bamosa AO, Ali BA, al-Hawsawi ZA. ; The effect of thymoquinone on blood lipids in rats. Indian J Physiology Pharmacol. 2002 Apr; 46(2): 195-201.
6. Zaoui, A., Cherrah, Y. et al. (2000). Diuretic and hypotensive effects of Nigella sativa on the spontaneously hypertensive rat. Therapie London. Mai Juin 55(3): 379-382
7. Gilani, A.H., Q. Jabeen and M.A.U. Khan, 2004. A review of medicinal uses and pharmacological activities of *Nigella sativa*. Pak. J. Biol. Sci., 7: 441-451.
8. Badary OA, Abdel-Naim AB, Abdel-Wahab MH, Hamada FM. (2000); The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. Toxicology
9. Al-Ghamdi MS; The anti-inflammatory, analgesic and antipyretic activity of Nigella sativa. J. Ethnopharmacol. 2001 Jun; 76(1):45-8.
10. Al-Awadi F, Fatania H, Shamte U.; The effect of a plants mixture extract on liver gluconeogenesis in streptozosin induced diabetic rats.; Diabetes Res. 1991 Dec;18(4):163-8.
11. Aqel, M. (1992a) The calcium antagonistic effect of the volatile oil of Nigella sativa seeds. Dirasat Series B Pure and Applied Sciences 19(1): 119-133. Dep. Anat., Fac. Med., Anat. /Smooth Muscles, Univ. Aiwa, USA.
12. El, T. K. E. H., M. M. S. Ashour, et al. (1993). The cardiovascular actions of the volatile oil of the Black Seed (Nigella sativa) in rats: Elucidation of the mechanism of action
13. Aqel, M. (1992b). The relaxing effect of the volatile oil of Nigella sativa seeds on vascular smooth muscle. Dirasat Series B Pure and Applied Sciences 19(2): 91-100.
14. Pearson TA, Blair SN, et al (2002) AHA Guidelines for primary prevention of cardiovascular disease and stroke. American Heart association Science Advisory and Coordinating Committee. Circulation.106:388-391.
15. Abdul Sattar, Allah Ditta, Muhammad Tayyib, Muhammad Ashraf.Estimation of serum lipids in albino Rats fed on palm oil and atherogenic diet and Nigella sativa. Pakistan Postgrad Med J Sep 2003; 14(3):121-4.
16. El-Dakhakhny M (1963): Studies on chemical constitution of Egyptian N sativa L seeds II. The Essential oil. Planta Med, 11; 465-470.
17. Enomoto S, Asano R, Iwahori Y, Narui T, Okada Y, Singab AN, Okuyama T.; Hematological studies on black cumin oil from the seeds of Nigella sativa L; Biol. Pharm Bull. 2001 Mar; 24 (3): 307-10.
18. Chaudhary et al 1996 Nigella sativaL. Oil protects against induced hepatotoxicity and improves serum lipid profile in rats. Arzneimittel Forschung, 50: 832-836.
19. Kumaranayaka et al (1997). The effect of Nigella sativa oil on blood lipids. Indian J. Physiol. Pharmacol., 46: 195-201.
20. Goodman and Gilman's The pharmacological basis of therapeutics (11th edition, Chapter 35, Drug therapy for hypercholesterolemia and dyslipidemia)
21. O'Driscoll, G.Greenand Taylor R.R. Simvastatin, an HMG Co A reductase inhibitor, improve endothelial function within one month. Circulation, 1997, 95:1126-1131.
22. Bustos C.,Hernandez Presa, et al. HMG CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis Am. Coll.Cardiol.1998, 32:2057-2064.
23. Hussein, O., Rosenblat, M. et al. (1997) Reduced platelet aggregation after fluvastatin therapy is associated with altered

platelet lipid composition and drug binding to platelets.Br.J.Clin. Pharmacol

24. Libby, P. Aikawa, Inflammation in atherosclerosis, Nature, 2002, 420:868-874
25. 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 atorvastatin, a new HMG-CoA reductase inhibitor. Arterioscler Thromb Vasc Biol 1995; 15:678-82.