To study the anti-hypertensive and lipid-lowering effects of garlic as add-on therapy to amlodipine in patients of hypertension with obesity

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ABSTRACT

Background: To study the anti-hypertensive and lipid-lowering effect of aged garlic extract as add-on therapy to amlodipine in patients of hypertension with obesity.

Methods: A randomized, prospective, open-labelled study of 90 days duration was undertaken at department of pharmacology, SGRDIMSAR, Amritsar. Patients of hypertension with obesity attending out-patient department of Medicine, SGRDIMSAR, Amritsar and fulfilling the inclusion criteria were enrolled. Patients were allocated into two groups treated with either amlodipine alone or Aged Garlic Extract (capsule in dose of 250 mg twice daily) along with amlodipine. A total of 60 patients successfully completed the study.

Results: At the end of study period of 90 days, a highly significant (p<0.001) reduction was seen in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients taking AGE along with amlodipine. On comparison with group taking amloidipine alone, difference of SBP was highly significant (p<0.001) in patients taking AGE along with amlodipine, but difference of DBP was not significant (p>0.05) between these two groups. There was a non-significant change (p>0.05) in lipid profile (serum total cholesterol, high-density lipoprotein cholesterol, triglycerides and low-density lipoprotein cholesterol) in patients taking only amlodipine but a significant reduction (p<0.05) in serum triglycerides, LDL and VLDL parameters of lipid profile in patients taking AGE along with amlodipine. Weight and BMI also reduced significantly (p<0.01) in patients taking AGE along with amlodipine.

Conclusions: AGE has been shown to have anti-hypertensive and lipid-lowering properties suggesting that garlic can be valuable agent in patients having hypertension with obesity.

Keywords: Aged garlic extract, Blood pressure, Lipid, Obesity, Amlodipine

INTRODUCTION

Hypertension has been considered the most important risk factor for conditions like end-stage renal disease, stroke, congestive heart failure, vascular dementia and myocardial infarction. Hypertension has been defined by the Eighth report of the Joint National Committee (JNC 8) as systolic blood pressure equal to or above 140 mm Hg and/or a diastolic blood pressure equal to or above 90 mm Hg.1 According to a global brief on hypertension by WHO, in 2008 approximately 40% of adults aged 25 and above i.e. as many as 1 billion people had been diagnosed with hypertension.2 In India, prevalence of hypertension has been estimated to be 20% in urban and 10% in rural population.3 Lifestyle risk factors like alcohol and tobacco abuse, physical inactivity, obesity and exposure to stress predispose to hypertension.4 Metabolic abnormalities like obesity, dyslipidemia and diabetes mellitus increase the risk of complications in hypertension.5 Association between obesity and hypertension has been well-documented and up to 60-70% of hypertension in adults can be directly attributable to truncal adiposity.4 Truncal obesity is observed to be more common in Indians5 and is associated with higher incidence of metabolic abnormalities like insulin resistance, dyslipidemia like elevated Low Density Lipoprotein-cholesterol (LDL-C), decreased High Density Lipoprotein-Cholesterol (HDL-C) and increased levels of inflammatory markers like C-reactive protein (CRP) and IL-6.6
Treatment of hypertension includes therapeutic lifestyle changes like control of diet and regular exercise initially. Anti-hypertensive drugs are indicated when lifestyle changes of at least 3 months fail to achieve adequate blood pressure control or in stage 2 hypertension or in the presence of end-organ damage. Among the various classes of anti-hypertensive drugs, thiazide diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and β-blockers, have all shown to reduce complications of hypertension and may be used for initial single drug therapy. CCBs are lipid neutral and effective anti-hypertensive drugs and are generally well-tolerated with minimal adverse effects like peripheral edema, flushing, and headache.

Amlodipine, a dihydropyridine CCB, is an efficacious blood pressure lowering agent. Despite adequate treatment with an effective antihypertensive agent like amlodipine, BP may remain uncontrolled. A higher dose of amlodipine is more likely to cause side effects like ankle edema and reflex tachycardia. Moreover hypertension in the presence of risk factors like obesity, dyslipidemia, atherogenesis and inflammatory states, necessitates the need for alternative therapy that has beneficial effects on cardiovascular risk profile and also have minimal side-effects.

Alternative therapy with anti-hypertensive and lipid-lowering effects has been extensively researched recently. Garlic (allium sativum) has been reported to have a beneficial effect in patients with hypertension with dyslipidemia. Aged Garlic Extract (AGE), which is processed for more than 10 months, is less irritating and does not produce the harmful effects of raw garlic like garlic taste and gastric irritation. The beneficial effects of AGE on cardiovascular risk profile include antihypertensive, lipid-lowering, weight-reducing and antioxidant. AGE is rich in an active and stable compound S-allylcysteine (SAC) along with other compounds like S-allylmercaptocysteine (SAMC), S-ethylcysteine (SEC), S-propylcysteine (SPC), lipid-soluble sulfur compounds, phenolic acids, flavonoids and other beneficial nutrients.

Adverse effects of AGE are reported to be mild and may occasionally cause bloating, flatulence, reflux, constipation, difficulty in swallowing and dry cough. Because of anti-platelet effects, AGE should be used cautiously in people using anti-platelet medications like warfarin and aspirin.

Findings from above studies indicate that AGE can be a valuable drug in the management of blood pressure and dyslipidemia. This study was planned to evaluate the anti-hypertensive and lipid-lowering effects of AGE along with amlodipine in patients of hypertension with obesity.

**METHODS**

This was an open-labelled, randomized, prospective study of 90 days duration conducted on 60 patients of hypertension with obesity of either sex. Patients visiting the Medicine OPD at Sri Guru Ram Das Charitable Hospital attached to Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar were enrolled. The institutional ethical clearance was obtained prior to the conduct of study. The selection of the patients was done on the basis of inclusion and exclusion criteria.

**Inclusion criteria**

Male or Female patients aged 30 – 60 years with stage 1 or stage 2 hypertension taking Tablet Amlodipine 5 mg/10 mg once daily and having BMI ≥ 25 kg/m² with deranged lipid profile.

**Exclusion criteria**

Patients requiring lipid lowering therapy or development of any clinical condition necessitating change in treatment, presenting with history of bleeding disorders, history of surgery within past 6 weeks, pregnancy, drug abuse, steroid treatment, hypersensitivity reaction to amlodipine or AGE, cardiovascular disease like ischemic heart disease, congestive heart failure, diabetes mellitus, thyroid disorder, hepatic disorder or renal disorder or on any other anti-hypertensive drug other than amlodipine were excluded from the study.

Written informed consent was obtained from all the enrolled patients, and the risks of the treatment were explained to patients in their own language. Patients were randomly divided into two groups of 30 each.

Group I (Control) patients were given Tablet Amlodipine 5 mg once daily after breakfast. If blood pressure was not controlled for one month, then dose was increased to 10 mg once daily.

Group II (Cases) patients were given the test drug i.e. Cap. Lasuna 250 mg twice daily after meals along with Tablet Amlodipine 5 mg once daily after breakfast. If blood pressure was not controlled for one month, then dose of tablet amlodipine was increased to 10 mg once daily.

The test drug used was Aged Garlic Extract formulation available as Capsule LASUNA in the dose of 250 mg twice a day after meals. The dose of Aged Garlic Extract administered in this study was adopted using information from literature provided by the manufacturer of Capsule Lasuna i.e., The Himalaya Drug Company, Bangalore, India. Patients were advised to undertake appropriate diet control and regular exercise as per latest guidelines for hypertension, obesity and dyslipidemia. They were also asked to exclude garlic from their diet.
Patients were regularly evaluated for systolic blood pressure (SBP) and diastolic blood pressure (DBP) during their visits to medicine OPD on 0, 7, 21, 45, 60 and 90 days. Their body weight and Body Mass Index was recorded at the start of study on day 0 and the end of study on day 90. Patients were investigated for lipid-profile consisting of serum Total Cholesterol (estimated by CHOD-PAP method), Triglyceride (estimated by GPO-PAP method), High density lipoprotein-cholesterol (estimated by PEG-CHOD-PAP method), Low density lipoprotein-cholesterol (calculated using Friedewald’s equation) and Very low density lipoprotein cholesterol (calculated using Friedewald’s equation) on day 0 and 90 i.e. at the beginning and the end of the study. Detailed record of their signs, symptoms and side effects was maintained.

Statistics

Student’s ‘t’ test was performed on data generated from the study. Results were tabulated in form of mean ± S.D. and the level of significance was determined as its ‘p’ value with p > 0.05 taken as not significant, p < 0.05 taken as significant at 5% significance level, p < 0.01 taken as significant at 1% significance level and p<0.001 taken as highly significant.

RESULTS

Study participants

Out of the 60 patients who completed the study, the number of males was 15 and the number of females was 45. The mean age of participants in group I was 46.76 ± 11.16 years and in group II was 50.23 ± 9.19 years. The mean body mass index (BMI) of patients in group I was 30.10 ± 3.99 kg/m² and in group II was 29.03 ± 3.38 kg/m² on day zero. There was no significant difference (p<0.05) in gender, age, body weight and body mass index in both the groups.

Blood pressure

The effects of amlodipine alone and AGE along with amlodipine on blood pressure is shown in Table 1 and Figure 1. In group taking amlodipine (Group I) alone, there was very significant reduction (p<0.01) in SBP of 4.50 ± 8.84 mm of Hg and significant reduction (p<0.05) in DBP of 3.33 ± 8.02 mm of Hg after 90 days of treatment. In group taking AGE along with amlodipine (Group II) a highly significant reduction (p<0.001) in SBP of 13.83 ± 13.11 mm of Hg and highly significant reduction (p<0.001) in DBP of 6.00 ± 8.13 mm of Hg was observed after 90 days of treatment.

On comparison of BP in both groups at the end of 90 days, a highly significant (p<0.001) difference of SBP and a non-significant (p>0.05) difference of DBP was seen in group taking AGE along with amlodipine as compared to group taking amlodipine alone (Table 1).

Lipid profile

The effect of amlodipine alone and AGE along with amlodipine on lipid profile after 90 days on treatment is shown in Table 2 and Figure 1. With amlodipine alone (group I), there was non-significant reduction (p>0.05) in total cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol and non-significant increase (p>0.05) in HDL-cholesterol at the end of the study. With AGE along with amlodipine (group II), total cholesterol reduction was 19.45 ± 54.02 mg/dl which was not significant (p>0.05); Triglycerides reduction was 30.76 ± 48.66 mg/dl which was very significant (p<0.01); HDL-cholesterol increase was 0.77 ± 6.58 mg/dl which was not significant (p>0.05); LDL-cholesterol reduction was 8.16 ± 39.6 mg/dl which was significant (p<0.05) and VLDL-cholesterol reduction was 6.15 ± 9.73 mg/dl which was very significant (p<0.01) by the end of the study.

**Table 1: Intergroup comparison of systolic blood pressure and diastolic blood pressure.**

| Study duration (Days) | Systolic BP | Diastolic BP |
|-----------------------|-------------|--------------|
|                       | Group I (Control) | Group II (Cases) | Intergroup comparison | Group I (Control) | Group II (Cases) | Intergroup comparison |
| 0                     | 136.50 ± 11.82 | 138.16 ± 11.77 | -1.66 ± 3.04<sup>NS</sup> | 85.66 ± 7.73 | 86.66 ± 6.60 | -1.00 ± 1.85<sup>NS</sup> |
| 7                     | 131.63 ± 12.26 | 128.00 ± 9.96 | 3.63 ± 2.88<sup>NS</sup> | 81.56 ± 6.2 | 83.66 ± 6.14 | -2.10 ± 1.59<sup>NS</sup> |
| 21                    | 130.33 ± 10.66 | 127.00 ± 10.55 | 3.33 ± 2.73<sup>NS</sup> | 82.83 ± 6.11 | 81.16 ± 6.90 | 1.66 ± 1.68<sup>NS</sup> |
| 45                    | 131.83 ± 7.48 | 127.00 ± 7.49 | 4.83 ± 1.93* | 83.00 ± 4.66 | 81.33 ± 5.07 | 1.66 ± 1.25<sup>NS</sup> |
| 60                    | 131.00 ± 8.03 | 126.00 ± 6.74 | 5.00 ± 1.91* | 81.66 ± 4.61 | 80.33 ± 4.90 | 1.33 ± 1.22<sup>NS</sup> |
| 90                    | 132.00 ± 7.02 | 124.33 ± 6.26 | 7.66 ± 1.71*** | 82.33 ± 4.3 | 80.66 ± 4.49 | 1.66 ± 1.13<sup>NS</sup> |

<sup>NS</sup>(p>0.05; Not Significant); *(p<0.05; Significant at 5% significance level); ***(p<0.01; Significant at 1% significance level); ***(p<0.001; Highly significant)
However, on comparison of total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol in both groups, it became evident that the difference was statistically not significant (p>0.05) at the start as well as at the end of the study (Table 2).

**Body weight and BMI**

The effect of amlodipine alone and AGE along with amlodipine on body weight and BMI after 90 days on treatment is demonstrated in Table 2. In group taking amlodipine alone (Group I), the reductions of body weight (0.13 ± 2.44 kg) and BMI (0.14 ± 0.95 kg/m²) were not significant (p>0.05) at the end of the study on day 90. In group taking AGE along with amlodipine (Group II), the reductions of body weight (2.40 ± 3.92 kg) and BMI (1.00 ± 1.71 kg/m²) at the end of the study on day 90 were also not significant (p>0.05). Comparison of body weight and BMI in both the groups demonstrated that the difference was statistically not significant (p>0.05) by the end of the study.

Table 2: Intergroup comparison of lipid profile, body weight and body mass index.

| Parameter            | Start of study (Day 0) | End of study (Day 90) |
|----------------------|------------------------|----------------------|
|                      | Group I (Control)      | Group II (Cases)     | Intergroup comparison | Group I (Control) | Group II (Cases) | Intergroup comparison |
| Total cholesterol    | 216.36 ± 43.11         | 224.39 ± 47.6        | -8.02 ± 11.73NS       | 215.52 ± 44.76    | 204.94 ± 57.4    | 10.58 ± 13.3NS       |
| Triglycerides        | 203.66 ± 59.96         | 203.68 ± 65.2        | -0.02 ± 16.17NS       | 195.07 ± 74.93    | 172.92 ± 58      | 22.15 ± 17.3NS       |
| HDL                  | 42.49 ± 7.34           | 45.46 ± 9.45         | -2.96 ± 2.18NS        | 42.69 ± 9.63      | 46.23 ± 9.41     | -3.54 ± 2.45NS       |
| LDL                  | 133.13 ± 38.48         | 154.26 ± 31.45       | -21.13 ± 9.08NS       | 133.73 ± 41.84    | 142.85 ± 30.79   | -7.17 ± 9.50NS       |
| VLDL                 | 40.70 ± 12.05          | 40.73 ± 13.04        | -0.03 ± 3.24NS        | 39.1 ± 14.96      | 34.58 ± 11.6     | 4.51 ± 3.45NS        |
| Weight               | 74.36 ± 9.89           | 72.13 ± 9.28         | 2.23 ± 2.47NS         | 74.23 ± 10.42     | 69.73 ± 7.95     | 4.50 ± 2.39NS        |
| BMI                  | 29.33 ± 2.95           | 29.03 ± 3.38         | 0.29 ± 0.81NS         | 29.18 ± 3.00      | 28.03 ± 3.44     | 1.15 ± 0.83NS        |

Table 3: Incidence of adverse drug reactions in Group I and Group II.

| Adverse Drug Reactions | Group I (n=30) | Group II (n=30) |
|------------------------|---------------|-----------------|
|                        | Number (% of n) |                  |
| Total                  | 4 (13.3%)      | 6 (20%)         |
| Epistaxis              | 0             | 0               |
| Bloating               | 2 (6%)         | 1 (3%)          |
| Abdominal pain         | 0             | 0               |
| Headache               | 0             | 0               |
| Somnolence             | 0             | 0               |
| Dizziness              | 0             | 0               |
| Ankle edema            | 2 (6%)         | 1 (3%)          |
| Irritability           | 0             | 2 (6%)          |
| Amenorrhea             | 0             | 1 (3%)          |
| Numbness of feet       | 0             | 1 (3%)          |
| Fatigue                | 0             | 0               |
| Any other              | 0             | 0               |

**Safety and tolerability**

A total of four patients (13.3%) taking amlodipine alone and six patients (20%) are taking AGE along with amlodipine reported adverse drug reactions (Table 3). None of the adverse events reported during this study were serious. Two patients reported irritability after taking AGE for one month and withdrew themselves from the study.

**DISCUSSION**

In the present study, the effects of aged garlic extract (AGE) with anti-hypertensive drug, amlodipine on blood pressure, lipid profile, weight and BMI were observed to be beneficial in patients of hypertension with obesity.

**Blood pressure**

In our study, AGE along with amlodipine produced highly significant reduction (p<0.001) in the SBP and
DBP by the end of 90 days. AGE along with amlodipine produced reduction in BP of 13.83/6.00 mm of Hg. The BP reduction with AGE along with amlodipine was highly significant (p<0.001) for SBP and non-significant (p>0.05) for DBP as compared to amlodipine alone. It has been proposed that AGE lowers blood pressure by affecting blood vessel elasticity.20 Other factors proposed include stimulation of production of intracellular nitric oxide and hydrogen sulphide, and inhibition of production of angiotensin II, which result in vasodilatation and reduction of BP.21

Similarly, various studies have reported anti-hypertensive effects of AGE in patients of hypertension. Rao et al22 in their study enrolled hypertensive subjects in two groups of 30 each, one group was given garlic extract plus amlodipine and other group was given amlodipine alone for 8 weeks. Their results indicated statistically significant reduction (p<0.05) in both systolic and diastolic blood pressure in combination group as compared to amlodipine group.22 Their results are in concordance with those in the present study showing significant reduction in BP in patients taking AGE along with amlodipine. Reid et al in a double-blind placebo-controlled trial involving 50 patients of treated but uncontrolled hypertension (SBP ≥ 140 mm of Hg at baseline), documented a significant lowering of SBP of 10.2 ± 4.3 mm of Hg (p = 0.03) with AGE as compared to placebo over a 12-weeks study period.23

Steiner et al in a double-blind crossover study in 1996 when compared the effect of aged garlic extract with placebo on 41 men, demonstrated a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure in response to AGE.24 This finding is similar to those in the present study that demonstrated a significant reduction of SBP whereas a modest reduction of DBP in group taking AGE along with amlodipine. Similarly, Qidwai and Ashfaq in their meta-analysis including 6 studies on 341 patients of hypertension have documented significant beneficial effects of AGE on BP of hypertensive patients.25 However, Seo et al in their comparative study on 30 post-menopausal women observed that there was beneficial but not significant change in blood pressure with AGE over a period of 12 weeks.26

**Lipids**

Our data confirms initial observations suggesting a beneficial effect on lipid profile. In group receiving AGE along with amlodipine, reduction in triglycerides was very significant (p<0.01), in LDL-cholesterol it was significant (p<0.05) and in VLDL-cholesterol it was very significant (p<0.01) by the end of the study. In comparative analysis day 90, it became evident that the difference between the lipid parameters was statistically non-significant (p>0.05).

Many short term studies have investigated the lipid-lowering effect of aged garlic extract. AGE has shown to inhibit HMG-CoA reductase, which is involved in cholesterol synthesis and exhibit anti-oxidant properties.27 AGE inhibits lipid oxidation and oxidative modification of LDL-cholesterol, thus lowering the levels of circulating LDL-cholesterol.20,28,29

Kumar et al in their open-labelled, prospective study on 60 patients of type 2 diabetes mellitus and obesity, observed a significant decrease in total cholesterol, triglycerides and LDL-cholesterol, and a significant increase in HDL-cholesterol with metformin alone and with AGE along with metformin; however, the reductions in total cholesterol, triglycerides and LDL-cholesterol and increase in HDL-cholesterol was significantly greater with metformin plus AGE.30 These results are in concordance with those in the present study.

Shah et al in their study, in which the three treatment groups was given AGE (as cap Lasuna), atorvastatin and AGE along with atorvastatin in patients suffering from hyperlipidaemia and/or obesity, observed that total cholesterol, LDL-cholesterol reduced and HDL levels increased significantly in group given atorvastatin and AGE along with atorvastatin but the difference was greater with AGE along with atorvastatin.30,31 They also observed non-significant reduction (p>0.05) of total cholesterol, HDL-cholesterol, triglycerides, VLDL-cholesterol and non-significant increase of LDL-cholesterol in patients given AGE alone.30 Gardner et al conducted a parallel design trial in 192 adults for six-months with the following four treatments: raw garlic, powdered garlic supplement, aged garlic extract supplement, or placebo. This study showed that there are no significant effect (p>0.05) on LDL-C or other plasma lipid concentrations in adults with moderate hypercholesterolemia.32

**Body weight and BMI**

The finding of present study conclude that a very significant reduction (p<0.01) of body weight and BMI was observed with AGE along with amlodipine. Amlodipine alone produced only small and non-significant reductions (p>0.05) in both body weight and BMI. In comparative analysis between both treatment groups on day 90, the difference of body weight and BMI was found to be statistically not significant (p>0.05).

Seo et al in their comparative study on 30 post-menopausal women observed that body weight was significantly decreased (p<0.05) in both AGE and exercise plus AGE groups compared to baseline.26 Gómez-Arbeláez et al in their crossover, placebo-controlled clinical trial to assess the effect of 1.2 g/day of AGE for 24 weeks of treatment (12 weeks of AGE and 12 weeks of placebo), observed that AGE significantly increased (p<0.05) the levels of adiponectin associated with abdominal obesity in patients of metabolic
syndrome. However their study showed non-significant reduction (p>0.05) in body mass index by the end of the study.

AGE accomplishes weight loss by interplay of many factors involving modulation of action of fat-producing genes and thermogenesis. A previous study suggested that garlic modulates lipid accumulation by suppressing the expression of genes that encode transcription factors and enzymes associated with adipocyte differentiation and adipogenesis in white adipose tissue. Ajoene, a breakdown product of allicin, induce apoptosis, decrease lipid accumulation in adipocytes and increase thermogenesis.

Safety and tolerability

Both AGE and amlodipine were well tolerated during the study and no new safety concerns were observed that were not known to occur with individual drug therapies. As shown in Table 3, total of four (13.3%) patients in group I and six (20%) patients in group II reported adverse drug reactions. All of these adverse drug reactions were considered mild to moderate. All ADRs were considered to result probably from treatment with AGE and amlodipine. Amenorrhea in one patient taking AGE resolved spontaneously in two weeks during study period and was considered as unlikely to result from its use. Two patients reported irritability after taking AGE and withdrew themselves from the study. Six patients withdrew themselves from the study for non-drug related causes like change of location and physician. All patients were followed-up for 2 weeks after the end of study. Therefore more adverse effects were observed in patients taking AGE.

CONCLUSION

In this study, AGE significantly lowered BP and lipids in patients of hypertension and obesity. AGE also enabled significant reduction in weight and BMI. Both AGE and amlodipine were well-tolerated. We can conclude that AGE is an efficacious and safe adjunct in lowering cardiovascular risk factors when given along with amlodipine in patients with hypertension, obesity and dyslipidemia.

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