

Does Garlic Supplementation Control Blood Pressure in Patients with Severe Coronary Artery Disease? A Clinical Trial Study

Marjan Mahdavi-Roshan,¹ Javad Nasrollahzadeh,¹ Ali Mohammad Zadeh,² and Ali Zahedmehr^{3,*}

¹Department of Guilan Interventional Cardiovascular Research Center, Heshmat Hospital, Guilan University of Medical Sciences, Rasht, IR Iran

²Radiology Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran

³Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Ali Zahedmehr, Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122357483, Fax: +98-2122360660, E-mail: Arashzahedmehr@yahoo.com

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Abstract

Background: Hypertension is one of the major risk factors for cardiovascular morbidities, including coronary artery disease (CAD).

Objectives: With interest on the important role of hypertension in the progression of CAD, this study was designed to estimate the effect of garlic powder tablets on the blood pressure (BP) in patients with severe CAD.

Methods: A randomized, placebo-controlled, clinical trial was conducted on 56 CAD patients, aged 25 - 75 years old. The patients were randomly divided into two groups: Galois groups (n = 27), receiving garlic powder tablet (400 mg garlic) twice daily and the placebo groups (n = 29), receiving placebo for 3 months. The BP was assessed at baseline and at the end of the study.

Results: During the 3 months study, in the placebo group, systolic BP (SBP) increased with 6.3 mmHg and diastolic BP (DBP) increased with 4.6 mmHg, changes which were significant. After the 3 months, the effect of garlic on SBP, after adjusting for baseline value, was significant, and this effect was more significant in hypertensive patients. Plasma lipids and lipoproteins did not change significantly in either the garlic or placebo groups, during the study. Tolerability, compliance and acceptability were high in all patients.

Conclusions: These results demonstrate that treatment with garlic-based drugs can be an effective treatment for controlling BP in CAD patients and has no interaction with other drugs that CAD patients take. Therefore, it may be considered as a safe adjunct treatment for this group of patients.

Keywords: Hypertension, Coronary Artery Disease, Garlic, Systolic Pressure, Diastolic Pressure

1. Background

Hypertension, which is defined as a systolic blood pressure (SBP) > 140 mmHg or a diastolic blood pressure (DBP) > 90 mmHg, is one of the major risk factors for cardiovascular morbidities, including coronary artery disease (CAD) (1).

By controlling BP in patients, one can control the progression of CAD. Hypertension affects one billion or one in three adults worldwide. Unfortunately, more than 50% of hypertensive individuals are unaware of their condition (2). Management of hypertension should include relevant lifestyle modifications, such as increased exercise, weight loss and dietary changes, which could incorporate dietary supplementation (2, 3).

Current medical therapy with standard antihypertensive medication is not always effective and leads to a large proportion of uncontrolled hypertension. In addition, side effects of treatment may be influence treatment adherence. For this reason, use of complementary and alternative therapies is high in patients (2).

Today's therapeutic effects of dietary products promote the development of disease treatment on the basis of natural products. Garlic has been used as both food and medicine for thousands of years, although there was little scientific support regarding its therapeutic properties, until recently (4, 5). Garlic contains at least 33 sulfur compounds, 17 amino acids, several enzymes, vitamins and minerals. Several of the sulfur-containing compounds, such as allicin, ajoene, S-allylcysteine, S-methylcysteine, diallyl disulfide and sulfoxides, may be responsible for the therapeutic effects of garlic (6, 7).

There are several garlic preparations on the market, including raw or cooked garlic, garlic powder, garlic oil and aged garlic extract. Dried garlic powder tablets are very similar to fresh garlic, with respect to chemical components. Like intact garlic cloves, dried garlic powder contains alliin, the inactive precursor of the biologically highly potent and strongly smelling allicin. The conversion of alliin to allicin depends on an enzyme, alliinase, which is present in fresh garlic, as well as in the dried gar-

lic powder tablets (8). Emerging evidence suggests that different garlic preparations, or its active components, could be useful for reducing cardiovascular risk and mortality from heart disease, which is the most common disease in the world (4, 9, 10). In the most of the previous studies the effect of garlic on BP, have been performed in healthy adults or hypertensive patients that took garlic supplements without any medical drug during study. Consequently, it is unclear whether standardized garlic preparations could provide a safe complementary treatment option for controlling BP in cardiovascular disease patients.

2. Objectives

With notice the important role of increased BP in the progression of CAD and, also, beneficial effect of garlic on health, here we assess the effect of garlic tablet, as an adjunct treatment, in patients with severe CAD that undergone angioplasty.

3. Methods

This study was a randomized, placebo-controlled, clinical trial. Subjects with severe CAD, candidates for angioplasty, were recruited from the Rajaei cardiovascular medical and research center, Iran University of Medical Sciences, Tehran, Iran, from August 2013 to April 2014. Inclusion criteria were: patients with CAD with one, two or three vessel stenosis, undergoing angioplasty, both men and women, aged 25 - 75 years old and with a body mass index (BMI) < 30 kg/m².

Exclusion criteria included: recent acute coronary syndrome (< 6 months), present smokers, diabetes, renal disease, BMI > 30 kg/m², consistent use of garlic in the last month and the use of antioxidant supplements. All subjects gave written and informed consent and the study was approved by the ethics committee of the national nutrition and food technology research institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran, registered under the number NCT01948453 at the clinical trials registration (ClinicalTrials.gov).

Following the baseline assessment, patients were randomized to receive either garlic powder tablet (equal to 400 mg garlic, 1200 µg allicin) twice daily or two placebo tablets/day for 3 months, in adjunct to their prescribed medications. Placebo tablets contained corn starch and were visually identical to the garlic tablets. Simple randomization was conducted using blocks of 10 sealed opaque envelopes, assigning five patients to receive garlic and five patients to receive placebo. Treatment was started within 3 days following angioplasty. Participants

in the two groups received dietary advice from a trained dietitian. The recommended diet was based on therapeutic life style change diet (11), containing 25% energy derived from fat, 20% from protein, and 55% from carbohydrate, with energy content based on the calorie requirement for weight maintenance that were estimated by the Mifflin-St Jeor equation (12). All subjects completed a take home 3-day food recall (two weekdays and one weekend) at baseline and end of intervention, and these records were verified by a nutritionist. Subjects' height, weight and BMI were measured at baseline and after the 3 months, by the same study coordinator. Physical activity was measured by physical activity questionnaire (13, 14) at baseline and after the 3 months.

3.1. Blood Pressure Monitoring

Blood pressure was measured by a trained research nurse, using a single calibrated mercury sphygmomanometer, with appropriate sized cuffs, at baseline and after the 3 months. The BP measurements were taken with the patient in a seated position, with their arm supported at heart level and after 5 minutes rest. The BP was recorded as two serial measurements, at intervals of 5 minutes. The mean of the two BP measurements was used in the analysis.

Hypertension was defined as SBP > 140 mmHg or DBP > 90 mm Hg, in a sitting position, on at least three different occasions.

3.2. Laboratory Analysis

Fasting blood samples were taken before angioplasty (baseline) and after 3 months. Laboratory measurements included plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, using commercially available kits (Pars Azmoon Sanat Pooya, Tehran, Iran). The LDL cholesterol was measured using a direct assay.

3.3. Statistical Analyses

Baseline characteristics for each of the two groups are described using means and standard error for continuous measures and percentages for dichotomous measures. For continuous variables, the Kolmogorov-Smirnov test was applied, to ensure normality. Baseline and post-treatment parameters were compared using a paired t test and an independent t-test for comparison of means between two groups, at baseline. Analysis of covariance was used for controlling of covariates (baseline value of triglycerides, SBP and DBP). The correlations between factors were determined by Pearson correlation coefficients. The level of significance set for all statistical analyses was P < 0.05. All

statistical analyses were performed using SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA).

4. Results

Prior to randomization, two subjects withdrew, since they returned to their own countries. Of the 70 subjects enrolled in the study, 35 subjects were randomized to the garlic group and 35 were randomized to the placebo (Figure 1). Fourteen subjects withdrew from the study following randomization, with 27 subjects completing study in the garlic group and 29 subjects in the placebo group.

Baseline characteristics were similar between the two groups (Table 1). The mean age of 56 the subjects that completed the study was 59.37 ± 1.28 years old. The frequencies of one, two and three vessel CAD were 61%, 35.1% and 3.9%, respectively.

Table 1. Baseline Characteristics of the Patients^a

Variable	Garlic Group (n = 27)	Placebo Group (n = 29)	P
Age, y	56.88 ± 1.67	61.68 ± 1.85	0.06
Sex, male, (%)	74.1	79.3	0.65
Body Weight, Kg	74.70 ± 2.94	69.75 ± 2.0	0.16
BMI, kg/m ²	26.09 ± 0.78	25.38 ± 0.54	0.45
PCI or CABG History	6 (22.2)	2 (6.8)	0.21
CAD			
Single Vessel Disease	18 (66.7)	19 (65.5)	
Two or Three Vessel Disease	9 (33.3)	10 (35.5)	0.47
Ejection Fraction, (%)	46.11 ± 1.17	42.93 ± 1.60	0.13
Hypertension	8 (26.9)	11 (37.9)	0.34
Medications			
Statins, n	27	29	-
Aspirin, n	27	29	-
Plavix, n	27	29	-
β-Blocker, n	25	29	0.30
ACE-I / ARB, n	27	29	-

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

^aValues are expressed as mean ± SE or No. (%) of subjects for dichotomous measures.

Plavix, aspirin, angiotensin-converting enzyme inhibitor / angiotensin receptor blocker, β-blocker and

Table 2. Daily Energy and Macronutrients Intake and Physical Activity in Patients^a

Variable	Baseline	3-m Follow-up	P ^b
Physical activity, METs h/day			
Garlic group (n = 8)	24.51 ± 1.17	24.26 ± 1.17	0.51
Placebo group (n = 11)	23.55 ± 1.29	23.31 ± 1.36	0.42
P	0.58	0.60	
Energy, kcal			
Garlic group (n = 27)	2547.1 ± 89.6	2566.1 ± 87.3	0.56
Placebo group (n = 29)	2397.8 ± 65.5	2450. ± 71	0.07
P ^b	0.17	0.30	
Carbohydrate, gram			
Garlic group (n = 27)	362.6 ± 15.4	365.1 ± 14.8	0.70
Placebo group (n = 29)	339 ± 11.2	347.3 ± 11.4	0.24
P	0.21	0.34	
Protein, gram			
Garlic group (n = 8)	114.5 ± 4.58	115 ± 4.44	0.71
Placebo group (n = 11)	108.1 ± 3.21	109.5 ± 3.67	0.65
P	0.25	0.29	
Fat, gram			
Garlic group (n = 8)	77.37 ± 2.05	80.36 ± 2.32	0.06
Placebo group (n = 11)	74.67 ± 1.95	76.54 ± 2.11	0.30
P	0.34	0.22	

Abbreviations: BP, blood pressure; METs, metabolic equivalents.

^aValues are expressed as mean ± SEM.

^bFor comparisons, t-test was performed

statins were prescribed to all 56 subjects of the study. There were no differences in total daily calories and macronutrient intake between groups, at the baseline of study, and, also, within groups. Both groups consumed the recommended diet (Table 2). There were no significant changes in body weight after 3 months, between both groups.

At the beginning of the study, the mean SBP and DBP of the 56 subjects that completed the study were 118.82 ± 2.01 and 75.53 ± 1.51 mmHg, respectively, and from 56 patients, 18 patients (32.1%) had hypertension. Also, there was no statistical significant difference in the number of patients that had hypertension between the two groups (Table 1).

After the 3 months, in the placebo group, SBP increased by 6.3 mmHg ($P = 0.002$) while DBP increased by 4.6 mmHg ($P = 0.015$) increased and these increases were not observed in the garlic group (Table 3).

In our study, when the baseline value of SBP was included as covariate in the analysis, the effect of garlic on SBP was significant (Table 3). The effect of garlic on BP in

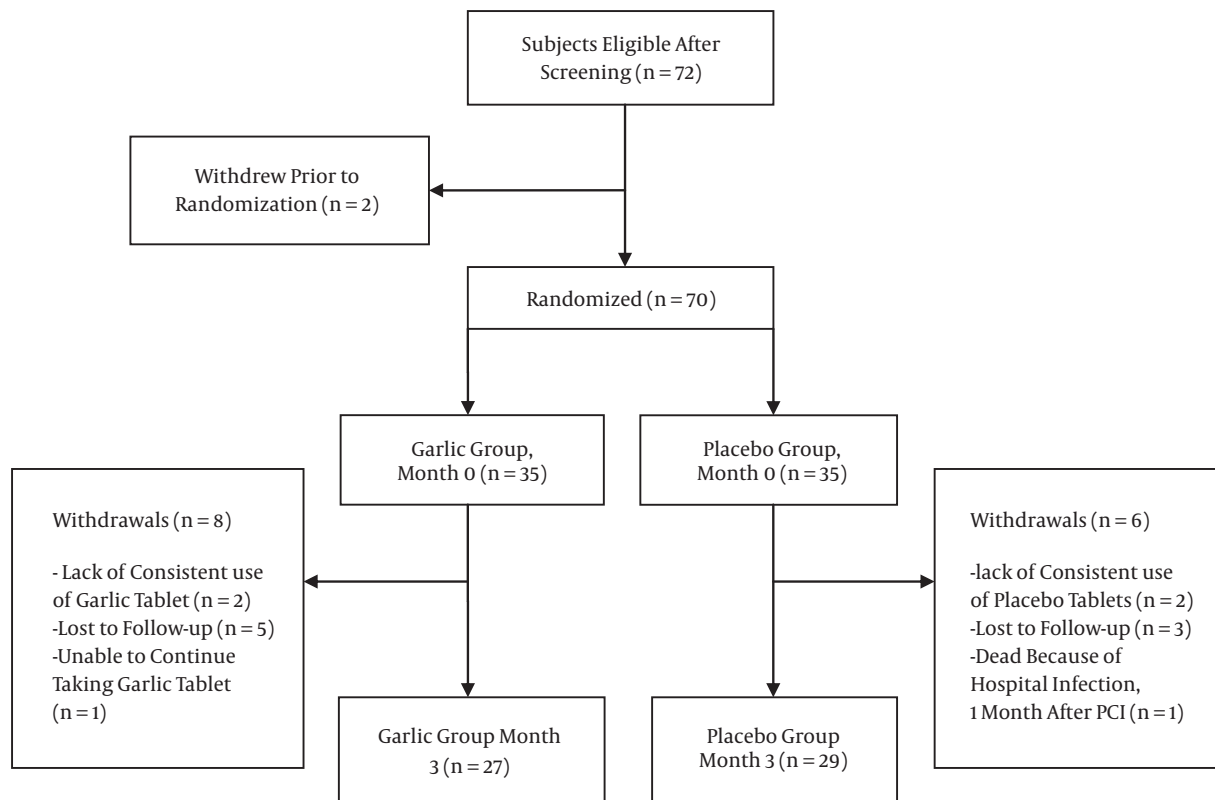


Figure 1. Participant Flowchart

hypertensive patients, compared to patients with normal BP, was more significant ($P = 0.002$). In secondary analyses, we included only subjects that had hypertension at baseline. In this group of patients, the mean changes in SBP between the two groups before and, also, after adjusting for baseline value of SBP, were significant (Table 3). In our study, there was no significant correlation between SBP or DBP and other CAD risk factors. In hypertensive patients, SBP was marginally correlated directly with BMI ($P = 0.08$) and DBP was correlated inversely with total cholesterol ($P = 0.02$) and HDL cholesterol ($P = 0.07$).

There were significant differences in the baseline levels of triglycerides between garlic and placebo groups (Table 4). No other significant baseline differences in the lipid, or lipoprotein values, were observed. There were within-group changes during therapy and, compared with baseline, all parameters measured at the end of the study increased, in both groups. There were no significant differences when mean changes in garlic-treated subjects were compared with mean changes in placebo-treated subjects.

4.1. Tolerability and Acceptability

Most of the participants found taking the tablets easy and acceptable. In the garlic group, one person had gastrointestinal complaints after 10 days of garlic tablet administration and, for this reason, did not continue the study. Most of the participants reported that they would be willing to continue taking the tablets after the trial was finished, if the treatment was effective.

5. Discussion

This trial suggests dry garlic powder tablet to be superior to placebo in lowering SBP in patients with severe CAD. A dosage of two capsules daily, containing 800 mg of dried garlic, significantly lowered SBP, compared with placebo, over 3 months, and the dose was well tolerated and highly acceptable.

The change in SBP, achieved in our study, is comparable with the results of other successful trials.

Ried et al. (2), in their study, showed that supplementation with garlic capsules containing 480 mg of aged garlic extract, for 12 weeks, lowered SBP by an average of 11.8

Table 3. Blood Pressure in Patients^a

Variable	Baseline	3-M Follow-Up	Changes From Baseline
All patients completed the study			
SBP, mmHg			
Garlic group (n = 27)	120 ± 3.0	121.1 ± 1.5	1.11 ± 2.6
Placebo group (n = 29)	117.6 ± 2.7	124 ± 1.6	6.31 ± 1.86
P	0.56	0.22	0.11
Adjusted P ^b	-	0.04	-
DBP, mmHg			
Garlic group (n = 27)	74.7 ± 2.2	78.8 ± 1.1	4.11 ± 2.3
Placebo group (n = 29)	76.2 ± 2.0	80.8 ± 0.8	4.6 ± 1.7
P	0.63	0.16	0.86
Adjusted P ^c	-	0.19	-
Subgroup of patients with hypertension at baseline			
SBP, mmHg			
Garlic group (n = 8)	135.7 ± 2.96	123.5 ± 3.8	-12.1 ± 2.1
Placebo group (n = 11)	126.4 ± 4	129 ± 2.5	2.6 ± 2.6
P	0.11	0.22	0.001
Adjusted P ^b	-	0.005	-
DBP, mmHg			
Garlic group (n = 8)	85.42 ± 3.9	81.42 ± 2.82	-4 ± 3.8
Placebo group (n = 11)	80.45 ± 2.4	81.81 ± 1.01	1.3 ± 2.6
P	0.27	0.88	0.24
Adjusted P ^c	-	0.65	-

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aValues are expressed as mean ± SEM.

^bFor comparisons, t-test was performed; Difference between groups in mean of SBP after adjusting for baseline SBP.

^cDifference between groups in mean of DBP after adjusting for baseline DBP.

mmHg, in patients with uncontrolled systolic hypertension.

A meta-analysis of 10 trial studies of the effect of garlic on SBP showed a significant difference between garlic and control groups, with garlic having a greater effect in reducing SBP by 4.56 mmHg, compared with placebo (15).

Although several clinical trials have suggested that garlic lowers SBP and/or DBP and has a beneficial effect in controlling BP, negative results have also been obtained in certain of the trials. A meta-analysis of eight controlled trials, with a total of 415 subjects, testing the same brand of dried garlic tablets, showed only small reductions in blood pressure. In this meta-analysis, only three of these trials were in hypertensive patients (16). Also, Simons et al., in a systematic review of the influence of trial quality on the effect of garlic on BP, concluded that the effect of garlic on BP cannot be ascertained (17). One reason for different result in

studies may be related to dose variation or varied types of garlic preparations (dried garlic powder, garlic oil or garlic extract) that may contain widely varying types of sulfur-containing phytochemicals due to the different methods of producing the preparations.

Possible mechanisms of the antihypertensive action of garlic can be related to its prostaglandin-like effects, which decrease peripheral vascular resistance (16). Garlic reduces prostaglandin E2 and thromboxane B2 levels (18). Also, the gamma-glutamylcysteines are the compounds in garlic that inhibit angiotensin-converting enzyme (19, 20). Garlic also inhibited endothelin-1 induced contraction, in a dose-dependent manner (21). Allicin and ajoene, in garlic, appear to inhibit inducible nitric oxide synthase in macrophages, reducing nitrite accumulation in atherosclerotic plaques and in hypoxic tissues (22, 23).

The population of our study included men and women

Table 4. Plasma Lipoproteins and lipid Profile in Patients

Variable	Baseline	3-M Follow Up	Changes From Baseline
Triglycerides, mg/dL			
Garlic group	85.25 ± 9.8	122 ± 11.8	35.03 ± 9.62
3-m follow-up	56.24 ± 4.3	99.92 ± 7.9	42.78 ± 6.52
P	0.008	< 0.001 ^a	0.31 ^a
Cholesterol, mg/dL			
Garlic group	108.1 ± 4.7	119.7 ± 5.0	11.8 ± 4.1
Placebo group	110.8 ± 5.4	129.1 ± 10.1	18.1 ± 6.2
p ^b	0.71	0.41	0.41
LDL-C, mg/dL			
Garlic group	54.18 ± 3.1	60.0 ± 3.2	6.1 ± 3.1
Placebo group	57.5 ± 3.7	66.2 ± 6.07	8.6 ± 3.7
P	0.49	0.38	0.61
HDL-C, mg/dL			
Garlic group	33.2 ± 1.7	38.3 ± 1.8	5.1 ± 1.1
Placebo group	36.1 ± 1.5	41.7 ± 1.8	5.5 ± 1.6
P	0.23	0.19	0.85

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

^a Analysis of covariance with baseline value, as covariate, was performed.

^b For comparisons, t-test was performed.

with severe CAD that undergone angioplasty and took garlic tablet in adjunct to conventional medical treatment. However, most of the previous studies have been performed in healthy adults or subjects with hypertension and without heart disease. Consequently, it was unclear whether standardized garlic preparations could provide a safe complementary treatment option for controlling BP in cardiovascular disease patients.

No BMI change was observed in our investigation and both groups received the same dietary advice and there were no differences in total daily calories and macronutrient intake, between groups.

In the present study, after 3 months, lipid and lipoprotein levels increased in both groups. However, this increased trend was lower in garlic group, compared to placebo group. The increase in lipid levels in our study may be related to different dosing of statin prescribed to patients before and after angioplasty. Based on the hospital management protocol of CAD patients undergoing angioplasty, high dose (80 mg/day) of atorvastatin was prescribed for all patients, for a period of 2 - 3 days before angioplasty and a constant maintenance dose (20 mg/day) for the rest of the study period. However, since the drug therapy protocol was relatively similar in all patients, it appears that the impact of medication on patients of garlic or

placebo groups was equal.

In conclusion, the results of our study suggest that 3 months treatment with garlic-based drug provides to be an effective and tolerable treatment for controlling BP in CAD patients and may be considered as a safe adjunct treatment for this group of patients.

Future large-scale trials are needed to investigate whether standardized garlic preparations could provide a safe complementary treatment option for controlling BP in CAD patients, in clinical practice.

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Footnotes

Authors' Contribution: Javad Nasrollahzadeh, Marjan Mahdavi-Roshan, Ali Zahedmehr and Ali Mohammad Zadeh conceptualized the study. Hospital coordination were performed by Ali Zahedmehr and Ali Mohammad Zadeh. Marjan Mahdavi-Roshan collected the data. Data were analyzed by Javad Nasrollahzadeh and Marjan Mahdavi-Roshan. Marjan Mahdavi-Roshan wrote

the manuscript and Javad Nasrollahzadeh performed critical revision of the manuscript for important intellectual content. Ali Zahedmehr and Ali Mohammad Zadeh contributed to reviewing the manuscript. All authors read and approved the final manuscript.

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