Significance of Garlic and Its Constituents in Cancer and Cardiovascular Disease

Aged Garlic Extract May Be Safe for Patients on Warfarin Therapy[1,3]

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ABSTRACT   Garlic has been known to have antiplatelet properties. Because of the lack of major clinical data regarding the safety of concomitant use of garlic supplements and anticoagulants, we decided to evaluate the safety of using garlic extract along with oral anticoagulation therapy. During this project we tested aged garlic extract (AGE), a commercial garlic preparation, with warfarin (Coumadin). Sixty-six (66) patients were screened for a double-blind, randomized, placebo-controlled pilot study. Fifty-two (52) patients were randomized for the project. Forty-eight patients (30 men and 18 women, with a mean age of 56 ± 10 years) completed the study. Eighteen patients (14 before randomization, 4 after randomization) were dropped from the study. The study medication (AGE or placebo) was administered at a dose of 5 mL twice a day for 12 wk. Potential bleeding and thromboembolic episodes were monitored. There was no evidence of increased hemorrhage in either the placebo or the AGE group. Adverse events included headache, fatigue, colds, and dizziness. However, no significant difference was found in the incidence of these minor adverse events between the groups. Thus, the adverse events are unlikely to be attributable to AGE. The results suggest that AGE is relatively safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy. Although the risk-benefit ratio of AGE use needs to be considered carefully when warfarin therapy is necessary, its positive effects may be beneficial to people with a high-risk background or who are taking cardiovascular medications.   J. Nutr. 136: 793S–795S, 2006.

KEY WORDS: • aged garlic extract • warfarin • oral anticoagulation therapy • S-allylcysteine

Aged garlic extract (AGE)[5] has been shown to be useful in many areas of health maintenance (1,2). It has been associated with improvement of the cholesterol profile (3,4), and specifically HDL, which positively affects cardiac risk (5–7), stimulates the immune system (8), prevents certain cancers (8), mitigates the effects of oxidants (9), normalizes blood pressure (3,10), and improves circulation (11,12). Due to garlic's known complications, its use has been cautiously discouraged for patients who are on anticoagulation therapy. Today, however, there are many antiplatelet agents, such as Plavix® (clopidogrel) and aspirin, that are prescribed routinely in conjunction with anticoagulants such as warfarin. Because garlic extracts have many potential medical benefits, the risk of increased bleeding, especially in patients on anticoagulation therapy, needs to be revisited (13).

A large number of patients are on AGE extract or other garlic-based agents for various medical indications such as hypercholesterolemia and hypertension. These patients may also suffer from ailments like deep vein thrombosis, which require anticoagulation therapy. Other than a study by Rosenfeld et al. (13) there are essentially no reliable data to help medical providers determine the disposition of garlic during anticoagulation treatment. Therefore, this study examines the safety of using AGE in patients on oral anticoagulation (warfarin) therapy.

We chose AGE because of the ample publications in peer-reviewed journals regarding its use. In addition, AGE is unique and different from other garlic preparations. The long-term

extraction process, called the aging process, is designed to eliminate odor, toxicity, and hemorrhage-causing, oil-soluble, sulfur compounds. Quality control is strictly followed in compliance with pharmaceutical Good Manufacturing Practices. The principal preparation for AGE appears in the U.S. Pharmacopoeia/National Formulary official monograph as Garlic Fluid Extract.

METHODS

Study population. This double-blind, randomized, placebo-controlled pilot study enrolled 66 patients. Fifty-two (52) patients were randomized to aged garlic extract (AGE) or a placebo. Inclusion criteria included participants diagnosed with deep vein thrombosis, cerebro-vascular accident, thrombosis, valvular heart disease, atrial fibrillation, or those with prosthetic heart valves. All were aged 18 y or above and were on warfarin therapy. The exclusion criteria included any significant medical conditions other than those mentioned, such as the presence of a terminal disease that could shorten the lifespan of the patient (e.g., cancer), a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, a history of hypersensitivity to garlic or study medication, the presence of anemia (<32 mg %), thrombocytopenia (platelets <75,000/mm^3), current drug abuse, active bleeding, uncontrolled hypertension, prior treatment with garlic or any related products within 3 mo, and treatment with any investigational drugs within 30 d prior to signing the consent. All participants of the study were volunteers and signed a consent form after a careful reading and review of the protocol.

Of the 66 enrolled patients, 48 (30 men and 18 women with a mean age of 56 ± 10 y) completed the protocol. The Institutional Review Board of Harbor-UCLA Research and Education Institute approved this project.

Aged garlic extract. AGE (Kyolic®), provided by Wakunaga of America, was formulated by soaking sliced raw garlic in aqueous ethanol solution for up to 20 mo at room temperature. The extract was filtered and concentrated under reduced pressure at low temperature. The procedure is described in the United States Pharmacopoeia/National Formulary monograph under Garlic Fluid Extract. The AGE used in this trial contained 305 g/L of extracted solids; S-allylcysteine, the most abundant water-soluble organosulfur compound in AGE, was present at a concentration of 1.47 g/L.

The administering of aged garlic extract. After obtaining consent, each patient was seen at baseline for an interview, a physical examination, and baseline blood tests. A urine pregnancy test was also done for each woman of childbearing age. Each subject had blood drawn after fasting for 12-h. For all subjects, a blood sample of ∼15 cc was drawn from an arm vein by the phlebotomist. The sample was centrifuged and the serum separated. Samples were stored at −70°C. After randomization, participants were started on either the AGE or the placebo at a dose of 5 mL twice daily for 12 wk. Participants were instructed to self-administer the study medication and keep the liquid containers refrigerated during the study.

At weeks 0, 4, and 8, a 1-mo supply of study medication (AGE or placebo) was given to each participant. Diaries were supplied to patients for monitoring warfarin and study-medication intake and compliance. The dose of warfarin was recorded for every encounter. At weeks 2, 6, and 10, patients were interviewed by telephone to collect any adverse-event information. At week 4, 8, and 12, patients were re-evaluated with a short physical examination and interview. Blood tests were performed.

Statistical analysis. Differences of all parameters were expressed to subtract the value at the end of the study (after 12 wks from entry). Comparisons of mean relative changes were made with the Student's *t* test.

Comparisons of all parameters between the AGE and placebo groups were made with the Student's *t* test. Continuous variables were presented as means ± SD. All statistical tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

After screening 66 patients, 52 were randomized. Thirteen (13) withdrew their consent, whereas 5 were lost at follow-up. Of the 48 patients who completed the study protocol, 22 took AGE, and 26 took the placebo. The baseline data between the groups of AGE and placebo is listed in **Table 1**. There was a significant difference in the number of gender subjects at the beginning of the study. Otherwise, there were no significant differences. The comparison differences of all parameters between AGE and placebo groups are indicated in **Table 2**. High-density lipoprotein cholesterol (HDL-C) increased among AGE patients compared with those on the placebo. None of the participants that completed the study had any major adverse event, including hemorrhage. Epistaxis, hemoptysis, hematuria, bloody stools, hemorrhage into organs, hemarthrosis, hematomas, or bruising were not noted either in the AGE or the placebo group.

DISCUSSION

Formal study has been lacking that would show the hemorrhagic risk of concomitant use of garlic with chronic anticoagulation therapy. Anecdotal cases allege a potential for garlic to interact with warfarin, inhibit platelet aggregation, and subsequently result in bleeding (15).

Anticoagulation therapy in itself carries the risk of bleeding complications. The presence of independent variables such as the duration of anticoagulation, number of comorbid conditions, and prolonged international normalized ratios may mitigate or potentiate risk (16–25). In this study, patients were on oral anticoagulation therapy on an outpatient basis for at least

TABLE 1

Baseline data at entry between the groups of AGE and placebo

	AGE	Placebo	P (2-tailed t test)
N	22	26	
Age, *y*	56 ± 11	55 ± 9	0.821
Gender, male, %	45%	77%	0.024[1]
Weight, *kg*	89 ± 44	91 ± 21	0.868
SBP, *mm Hg*	122 ± 23	127 ± 19	0.378
DBP, *mm Hg*	74 ± 17	82 ± 16	0.113
Glucose, *mg/dl*	137 ± 74	113 ± 45	0.184
TC, *mg/dl*	184 ± 36	184 ± 46	0.975
TG, *mg/dl*	221 ± 141	183 ± 110	0.289
HDL-C, *mg/dl*	43 ± 13	40 ± 10	0.349
LDL-C, *mg/dl*	104 ± 32	108 ± 38	0.702
Hemoglobin, *g/dl*	14.0 ± 1.8	14.8 ± 0.9	0.064
Platelet,	232 ± 75	236 ± 69	0.834
PT INR	2.4 ± 0.8	2.4 ± 1.1	0.779
Diseases			0.453[1]
Cardiac thrombosis, %	77	81	
Vascular thrombosis, %	23	15	
Combined[2], %	0	4	
Histories			
Hypertension, %	62	38	0.108[1]
Diabetes Mellitus, %	41	27	0.306[1]
Hypercholesterolemia, %	9	15	0.507[1]

[1] Chi-square test.
[2] Combined with deep venous thrombosis and atrial fibrillation; *n*, number of participants; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; PT INR, prothrombin time-international normalized ratio.

TABLE 2

Changes during 12 wks between the groups of AGE and placebo

	AGE	Placebo	P (2-tailed t test)
N	22	26	
Weight, *kg*	2.6 ± 8.9	0.2 ± 2.2	0.184
SBP, *mm Hg*	2.9 ± 18.7	0.7 ± 19.7	0.697
DBP, *mm Hg*	−0.5 ± 11.8	0.3 ± 13.7	0.829
Glucose, *mg/dl*	7.4 ± 34.9	9.9 ± 29.6	0.788
TC, *mg/dl*	8.4 ± 28.0	−4.1 ± 27.6	0.128
TG, *mg/dl*	27.9 ± 115.3	−4.0 ± 59.4	0.279
HDL-C, *mg/dl*	2.9 ± 7.9	−1.6 ± 6.7	0.038
LDL-C, *mg/dl*	2.6 ± 25.8	−1.6 ± 30.0	0.626
Hemoglobin, *g/dl*	−0.2 ± 0.6	0.0 ± 0.8	0.210
Platelet	0.1 ± 72.1	2.4 ± 35.4	0.887
PT INR	0.0 ± 1.2	0.2 ± 0.9	0.579
Incidence of hemorrhage, *n*	0	0	1.000
Dose of warfarin			0.939[1]
Increase, %	18	15	
Unchanged, %	73	73	
Decrease, %	9	12	

[1] Chi-square test. *n*, number of participants; SBP, systolic blood pressure DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; PT INR, prothrombin time-international normalized ratio.

12 wk. The indications for the use of warfarin were atrial fibrillation, cardiac valve replacement, pulmonary embolism, and deep vein thrombosis.

This trial found no bleeding associated with the concomitant use of AGE and oral anticoagulation therapy, which suggests that there is no blood-thinning synergism between them. This could be due to close observation and monitoring (biweekly telephone follow-ups and monthly study visits). Maintaining appropriate international normalized ratio levels may have precluded any untoward signs and symptoms from getting out of control. Gender differences did not affect the results significantly because neither AGE nor the placebo group had any episode of notable hemorrhagic complications.

Garlic is alleged to be associated with acquired platelet dysfunction that can cause bleeding in some situations. However, compared with other antiplatelet agents used routinely with warfarin for various indications, AGE is unlikely to be a more potent antiplatelet agent (26).

Clinical studies show the intake of *S*-allyl cysteine is followed by a decrease of fats or blood lipids, including triglycerides and serum cholesterol, inhibition of platelet aggregation, enhancement of circulation, and decrease in blood pressure.

The literature is replete with indications that show a positive effect of AGE on the lipoprotein profile (3–7). As anticipated, our study also showed a positive increase in the HDL fraction, but no decrease in the total cholesterol picture. This result may be caused by short-term consumption compared with previous studies. Again, the gender differences upon entering the study need to be considered. However, the finding is consistent with previous data in the literature as noted above.

This study demonstrated that there was no increase in the incidence of hemorrhages with AGE use in patients on oral anticoagulation (warfarin) therapy. The results suggest that use of AGE may be carefully administered along with anticoagulation therapy, provided that close monitoring is mandated (27). Further study is necessary to confirm the safety of AGE for patients on oral anticoagulation treatment.

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