

## Research and Professional Briefs

## Cranberry Does Not Affect Prothrombin Time in Male Subjects on Warfarin

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## ABSTRACT

There have been case reports suggesting that cranberry beverages may interact with warfarin. To date, no research study has been conducted to examine the potential interaction of cranberry and warfarin. The current study is a randomized, placebo-controlled, double-blind, crossover study to investigate the effect of cranberry juice on prothrombin time as assessed by the international normalized ratio (INR). Seven subjects with atrial fibrillation on a stable dose of warfarin for 3 months were randomized to consume 250 mL of cranberry juice for 7 days, then placebo for 7 days, or vice versa. The washout period was 7 days. The prothrombin time/INR was measured at baseline, and on days 2, 4, 7, 10, 14, 16, 18, 21, and 24. Data were analyzed by the Student *t* test for paired values. The baseline INR was  $2.28 \pm 0.54$  for the cranberry group and  $2.13 \pm 0.50$  for the placebo group. For all test points, the INR did not change significantly from baseline. At day 7 on cranberry juice, the INR was  $2.23 \pm 0.53$  for cranberry first group and  $2.16 \pm 0.40$  for placebo first group. The mean differences between the cranberry and placebo groups were not statistically significant. Our results suggest no significant interaction between the daily consumption of 250 mL cranberry juice and warfarin. When counseling patients on dietary changes necessary during warfarin treatment, it does not seem necessary to eliminate daily cranberry juice con-

sumption at amounts of 250 mL, but the INR should be followed up closely.

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The blood-thinning medication warfarin acts as a vitamin K antagonist and is widely used for the primary and secondary prevention of arterial and venous thromboembolism in patients with common cardiovascular and peripheral vascular diseases. The major side effect of anticoagulant therapy is hemorrhage, and considerable effort and resources are expended in maintaining warfarin doses in a safe and effective therapeutic dose range (1). The therapeutic index and safety of anticoagulation therapy is assessed through measurement of the prothrombin time, which is expressed as the international normalized ratio (INR). An INR of 2.0 to 3.0 is generally considered in the therapeutic range, and the risk of bleeding increases when the INR exceeds 4.0.

There are some well-known interactions of other drugs as well as foods with blood-thinning medications. The list of drugs that interact with vitamin K antagonists is constantly expanding (2), and patients are routinely counseled to either avoid or maintain relatively constant their intake of food sources rich in natural vitamin K, such as dark-green vegetables.

In 2003, a report from the United Kingdom's Committee on Safety of Medicines suggested that cranberry beverages might interact with warfarin medication by reducing its potency (3). The stated rationale was that the flavonoids in the fruit are known to inhibit cytochrome P450 activity, the enzymes used to break down warfarin, but there was no direct evidence in these cases of an effect of cranberry on cytochrome P450 activity or that such an effect would be of sufficient magnitude to affect INR in any of the cases studied.

Cranberries (*Vaccinium* spp.) are rich in a number of phenolic compounds, including proanthocyanidins, anthocyanins, flavonoids, and phenolic acids, with potential health benefits. The proanthocyanidins have been shown to reduce adhesion of bacteria to the bladder epithelium in animals, and studies are currently underway to definitively establish the benefit of cranberry extracts for the prevention of urinary tract infections in women (4,5). Studies have also shown that cranberry polyphenols are potent antioxidants and can inhibit oxidation of low-density lipoproteins (6,7).

This study was designed to test whether cranberry juice would adversely affect INR levels in a small number of well-studied subjects in which a prospectively random-

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**Table 1.** Timeline for intervention and international normalized ratio (INR) measurement for prothrombin time in a study to investigate the effect of cranberry juice on prothrombin time in patients with a common cardiovascular condition necessitating the use of warfarin

Group	Week 1	Week 2	Week 3	Week 4
Placebo	Placebo drink	Washout	Cranberry juice	
Cranberry	Cranberry juice	Washout	Placebo drink	Washout
	<b>Days</b>	<b>Days</b>	<b>Days</b>	<b>Days</b>
INR	0, 2, 4, 7	10, 14	16, 18, 21	24

ized, double-blind, control design was utilized. Patients with atrial fibrillation are commonly prescribed warfarin to prevent thromboembolism; therefore, a group of patients with atrial fibrillation on a stable dose of anticoagulant for 3 months was recruited into the present study to investigate the effects of cranberry juice consumption in typical amounts on INR in patients with a common cardiovascular condition necessitating the use of warfarin.

## METHODS

A double-blind, prospectively randomized crossover study design in two phases was used. Subjects with atrial fibrillation on a stable dose regimen of warfarin for at least 3 months before entry in the study were recruited. At baseline, subjects underwent a physical examination by the principal investigator. Routine blood chemistry, including complete blood cell count, chemistry panel, and renal and liver function tests, was performed. Subjects were excluded if they were consuming cranberry products more than five times per week or taking any medications known to interact with warfarin, including recent use of aspirin or other anti-inflammatory medications. Subjects with heart rates of less than 50 or greater than 100 and those with symptoms or signs of congestive heart failure were excluded. Subjects with uncontrolled hypertension, defined as an average of three consecutive seated blood pressure measurements with systolic and/or diastolic blood pressure greater than 150/90 mm Hg, were excluded. Subjects with serious illnesses, including pulmonary, renal hepatic, endocrinologic, hematologic, neurologic, psychologic, or gastrointestinal abnormalities were excluded, as were any subjects with significantly abnormal serum chemistry or hematology at screening. Subjects consuming alcohol in excess of 14 alcoholic beverages per week over the 3 months before screening were also excluded. The study protocol was approved by the Ethics Committee of University of California Los Angeles, and subjects were recruited by public advertisement. Eight volunteers were recruited, and written consent was obtained. A total of 250 mL of cranberry juice or placebo was provided because this volume of cranberry juice had previously been shown to be effective in preventing urinary tract infections (4,5).

The placebo and cranberry juice cocktail were provided by the Cranberry Institute (East Wareham, MA). The cranberry placebo was formulated using artificial colored pigments and did not contain any cranberry marker compounds. Both were packaged in identical 250-mL paperboard juice boxes. The products were formulated from cranberry, noncranberry, and nonfruit ingredients, all of

which were of food-grade quality for human consumption. Packaging occurred under carefully controlled quality assurance and quality control programs. The products were packed under similar conditions and in the same packaging.

Subjects were randomly assigned to receive either placebo or cranberry juice for 1 week, followed by a 1-week washout period. In the next week, the other beverage (cranberry juice or placebo, respectively) was consumed so that all subjects received either cranberry juice or placebo in random order (Table 1). During the week of washout, subjects were instructed not to consume any cranberry products. All subjects were instructed to maintain their warfarin dose and not to change any other dietary or exercise habits.

Blood samples were obtained by venipuncture. Complete blood cell count, chemistry panel, and renal and liver function tests were performed at screening. INR was tested at screening, and on days 0, 2, 4, 7, 10, 14, 16, 18, 21, and 24 in the morning after breakfast. Blood was drawn into a test tube containing sodium citrate, mixed immediately, and analyzed by the University of California Los Angeles clinical laboratory.

Randomization was carried out using random probability drawn from uniform probability distributions. Probability values above 0.50 were assigned to group A, and probability values  $\leq 0.5$  were assigned to group B. Statistical power was calculated before the study to determine whether the sample size was sufficiently large to detect a difference that could affect outcome. With a sample size of seven using the clinical research design in which each subject served as his own control, a mean INR difference of 0.5 with an INR standard deviation of 0.2 would be detected with 80% power using a one-sided significance level of  $P=0.05$ . Normality was assessed using the Shapiro-Wilks test for normality using small samples (8). Both baseline and day 7 samples for placebo and cranberry groups, respectively, met the assumption of normality ( $P>0.05$ ) in which the hypothesis that the data met the assumption of normality could not be rejected.

The data for the INR values are expressed as mean values  $\pm$  standard deviation. Data were analyzed by the Student *t* test for paired values, and differences were regarded as statistically significant when *P* values were  $<0.05$ . Baseline was compared with day 7, and day 14 was compared with day 21.

## RESULTS AND DISCUSSION

Eight male subjects (three African American and five white) met the inclusion and exclusion criteria and were

**Table 2.** Age, sex, race, and comorbid conditions of study subjects at baseline in a study to investigate the effect of cranberry juice on prothrombin time in patients with a common cardiovascular condition necessitating the use of warfarin

	Age	Sex	Race	Comorbid conditions
1	64	Male	African American	Hypertension, hypercholesterolemia, gout, stroke
2	51	Male	White	
3	65	Male	African American	Hypertension, hypercholesterolemia
4	77	Male	White	
5	76	Male	White	Coronary artery disease, hypercholesterolemia
6	82	Male	White	Degenerative arthritis
7	63	Male	White	
8	73	Male	African American	Hypertension, hypercholesterolemia

randomized to the study. The average age was  $68.8 \pm 10.0$  years (Table 2). One subject in the group of cranberry followed with placebo withdrew after randomization because of transportation difficulties. The remaining seven subjects completed the study. None of the subjects reported any dose change of any of their medications, including warfarin, during the study period.

The baseline INR was  $2.28 \pm 0.54$  for cranberry group and  $2.13 \pm 0.50$  for placebo group. No significant difference ( $P=0.86$ ) between the groups at baseline was shown. In addition, no significant difference was seen between the two groups during the 7 days of cranberry juice consumption. At day 7, the INR was  $2.23 \pm 0.53$  for the cranberry juice group and  $2.16 \pm 0.40$  for the placebo group. For all test points in either group, the INR did not change significantly from baseline (Figure).

In September 2003, the United Kingdom's Committee on Safety of Medicines and the Medicines and Healthcare Products Regulatory Agency highlighted the possible interaction between warfarin and cranberry juice and advised patients taking warfarin to limit or avoid drinking cranberry juice (3). They had received eight reports since 1999 of a possible interaction that led to changes in the INR or bleeding: in one case the patient died, in four cases there was an increase in the INR or bleeding, in two cases the INR was unstable, and in one case the INR decreased (9). In the fatal case, the patient's previously stable INR increased to  $>50$  (therapeutic INR = 2.0 to 3.0). However, the patient had a poor appetite and ate nearly nothing, taking only cranberry juice as well as his regular medicine (digoxin, phenytoin, and warfarin). In another case of a patient with a prosthetic mitral valve taking warfarin, a persistently elevated INR was noted 2 weeks after the patient began to drink cranberry juice (almost 2 L/day). Subsequent surgery led to postoperative bleeding complications (10). The above cases are medically complicated, and many factors could have affected the INR other than cranberry juice. In addition, the patients had ingested large amounts of cranberry juice.

Foods rich in vitamin K may inhibit the anticoagulant effect, but generally substantial amounts are needed. Thus, 250 g of spinach or broccoli, eaten on a single occasion, does not affect the prothrombin time (11), whereas higher amounts, in the range of 400 g, exert an effect (11,12). Warfarin and other warfarin anticoagulants act by inhibiting the synthesis of vitamin K-dependent clotting factors, which include Factors II, VII, IX,

and X and the anticoagulant proteins C and S. An anticoagulation effect generally occurs within 24 hours after drug administration. However, the peak anticoagulant effect may be delayed by 72 to 96 hours. The duration of action of a single dose of warfarin is 2 to 5 days (13). This is reflected by standard clinical practice, which is adjustment of the warfarin dose every 5 days.

In a group of 11 subjects, Karlson and colleagues (11) studied the influence of the consumption of either 250 g broccoli, 250 g spinach, or 250  $\mu$ g vitamin K1 per day for 7 days on the effectiveness of warfarin treatment. It was determined that the maximum effects of the foods occurred at day 5. In another study, Pedersen and colleagues (12) also found that a diet high in vitamin K affected the plasma coagulant activity significantly on day 5. On the basis of general clinical practice and the above studies, a 7-day intake of cranberry juice should be sufficient to detect any possible interaction between cranberry and warfarin.

The current study used a crossover design in which subjects were randomly assigned to take 250 mL of placebo followed by cranberry juice or vice versa for the study period. Those subjects who ingested placebo first provided additional information on the stability of INR in these subjects with atrial fibrillation over a 1-week period. Those who consumed cranberry juice first showed that there were no residual effects of the cranberry juice on INR after the washout period and before consuming placebo.

The major limitation of the current study was the small sample size. However, it is clear from our study that this is not a general effect in every patient taking anticoagulants. The study does not eliminate the possibility of idiosyncratic susceptibility to the effects of cranberry juice on warfarin metabolism in individuals with genetic polymorphisms of the cytochrome P450 system. However, it does increase the need for more research in larger numbers of individuals before concluding that there is a causal relationship between cranberry juice consumption and the reported adverse events.

## CONCLUSIONS

Given the narrow therapeutic margin of warfarin, patients should be aware of which drugs, natural health products, and food products may be associated with interactions.

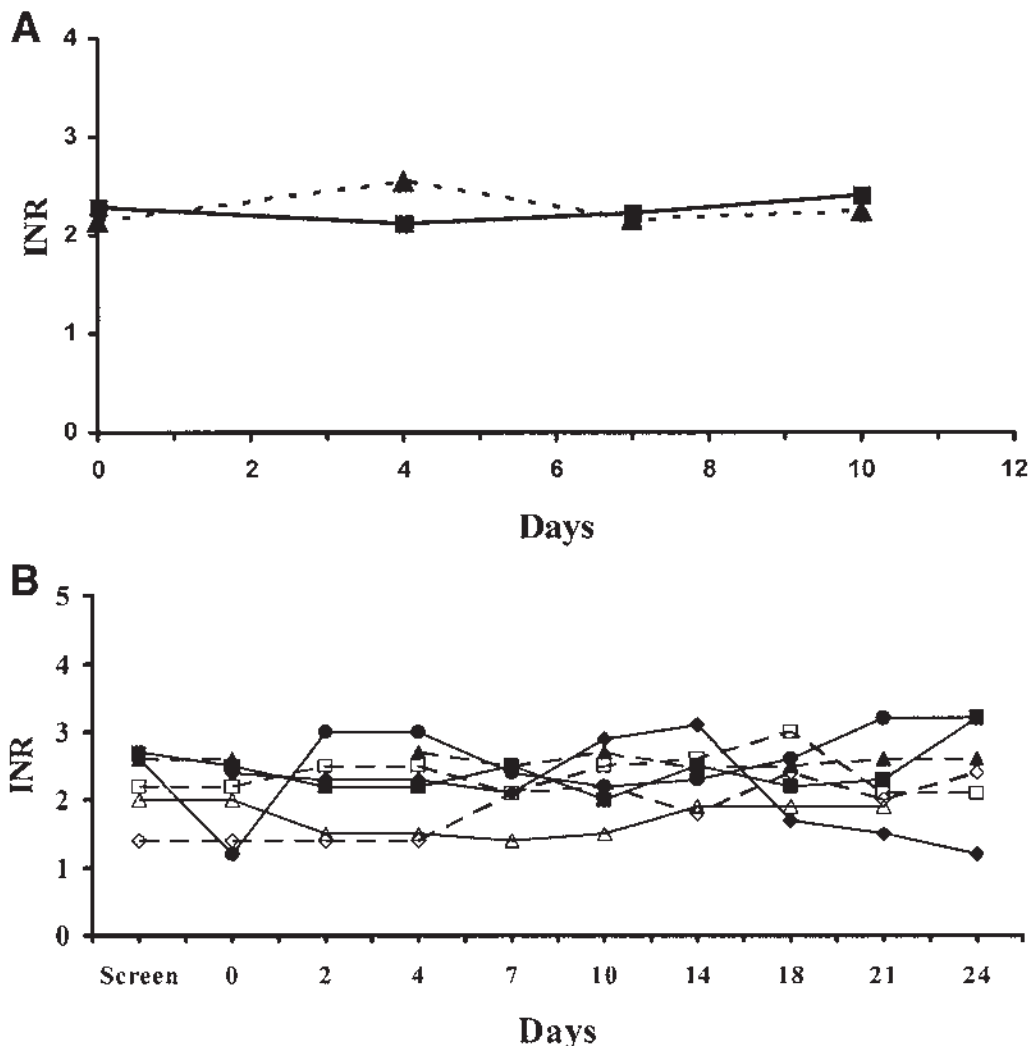


Figure. (A) Time response of international normalized ratio (INR) for placebo (□) and cranberry (■) groups during the time of cranberry juice ingestion. (B) Time response of INR for each subject during the entire study. Subject 2 (—◆—), subject 3 (—■—), subject 4 (—□—), subject 5 (—●—), subject 6 (- -◇- -), subject 7 (- -□- -), and subject 8 (—△—).

In the present study, we did not detect any significant interaction between daily consumption of 250 mL cranberry juice and warfarin. It does not seem necessary to eliminate cranberry juice consumption routinely in all patients on warfarin. Rather, modest dietary intakes of cranberry products should be emphasized with routine INR monitoring.

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