Is vitamin C superior to diltiazem for radial artery vasodilation in patients awaiting coronary artery bypass grafting?

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Objectives: We aimed to measure the vasodilating effects of vitamin C on the radial arteries of healthy subjects and to assess whether vitamin C is superior in this regard to diltiazem, a commonly used vasodilator in coronary artery bypass using radial conduits.

Methods: In a case-control study (study 1) oral single-dose vitamin C (2 g) was given to 15 healthy nonsmokers and 15 matched otherwise healthy smokers. In a randomized double-blind study (study 2) oral single-dose vitamin C (2 g, n = 15) and diltiazem (180 mg, n = 15) were compared in preoperative patients with coronary artery disease. We examined the dilation of the radial artery with high-resolution ultrasonography and measurement of the lumen surface and color Doppler images of the nondominant radial artery just before and 2 hours after drug administration.

Results: In study 1 both smokers and nonsmokers showed a significant increase in the lumen surface at 2 hours compared with at baseline ($P < .001$ and $P = .013$, respectively). The increase was larger in smokers (median, 37.5% vs 14.3%; $P = .004$). In study 2 both groups showed statistically significant increases in the lumen surface at 2 hours compared with at baseline ($P < .001$ and $P = .008$ for vitamin C and diltiazem, respectively). Vitamin C achieved a larger increase than diltiazem (median, 33.3% vs 18.2%; $P = .016$). In multivariate modeling the increase in lumen surface was independently predicted by use of vitamin C over diltiazem (+21.2%, $P = .007$), diabetes mellitus (+14.5%, $P = .085$), increased cholesterol (+26.2%, $P = .001$), and smoking history (+20.8%, $P = .017$).

Conclusions: Vitamin C is a potent acute vasodilator in both smokers and nonsmokers and is superior to diltiazem in preoperative coronary patients who need protection from vasospasm of the radial conduit.

The radial artery is increasingly used as a conduit for coronary artery bypass grafting because of reports of long-term patency, accessibility, and encouraging midterm results.¹⁻³ Calcium-channel antagonists, in particular diltiazem, or other vasodilators are used to prevent perioperative spasm of the graft.⁴⁻⁶ The choice of a potent vasodilator with minimal side effects appears to be an important parameter in ensuring the success of radial artery conduits.

Human coronary and peripheral arteries display abnormal endothelial function and loss of endothelium-dependent vasodilation in the presence of overt coronary

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artery disease or coronary risk factors.⁷⁻⁹ Ascorbic acid, or vitamin C, the main water-soluble antioxidant in human plasma¹⁰ has been shown to reverse endothelial dysfunction in patients with ischemic heart disease.^{11,12} It has also been shown to improve endothelial dysfunction in smokers¹³⁻¹⁵ and patients with diabetes,¹⁶ hypercholesterolemia,¹⁷ and hypertension,¹⁸ although not in a consistent manner.^{19,20} It is not known whether, given these observations, vitamin C could be used instead of calcium-channel blockers as a vasodilator in coronary surgery patients receiving radial artery conduits.

Vitamin C was studied in 2 groups of healthy volunteers with and without a history of smoking. Subsequently, in a randomized double-blind study vitamin C was compared with diltiazem in patients with coronary artery disease, as measured by using Doppler imaging 2 hours after administration.

Patients and Methods

Subjects

A total of 30 healthy subjects were enrolled in a case-control study evaluating the effects of vitamin C in smokers ($n = 15$) versus nonsmokers ($n = 15$, study 1). Exclusion criteria included known cardiovascular disease or the presence of any known coronary risk factors (other than smoking and family history). Subjects in the 2 groups were frequency matched for age. Subjects in both groups received vitamin C orally (2 g), and the effect on the radial artery was assessed 2 hours later by an evaluator who was blinded to the smoking status of the subject. The vitamin C dose was selected because it has been used in previous studies²¹ and is known to achieve 2.5-fold increases of plasma ascorbic acid in 2 hours.¹²

A total of 30 preoperative subjects with coronary artery disease who had been admitted to the Department of Cardiothoracic Surgery of the University of Ioannina were enrolled in a randomized, double-blind, parallel-arm trial comparing single-dose oral vitamin C (2 g) with oral diltiazem (180 mg, study 2). The effect of each drug on the radial artery was similarly assessed 2 hours after drug administration by a blinded evaluator. The randomization was performed by using a computer-generated code, and allocation concealment was ensured.

For both studies, all subjects had to refrain from smoking for at least 3 hours before the study to minimize any relevant effect of acute smoking. In addition, all subjects were instructed to refrain from the intake of caffeine-containing beverages within 24 hours before administration of the drug. No patients were receiving any vitamins. The collected information on each subject included demographics, as well as data on potential cardiovascular risk factors for the subjects enrolled in the randomized trial. Both studies received approval, and all subjects were enrolled after providing informed consent according to the hospital's ethics committee. No patients withdrew after providing informed consent.

Radial Artery Measurements

High-resolution ultrasound measurements and color Doppler images were taken by using an ultrasound device (color Doppler Acuson 128 XP/10 with 7-MHz linear transducer), and records of the lumen surface of the radial artery (nondominant) before the

drug administration were followed by using a measurement 2 hours later (Figure 1). All lumen surface areas (derived from the estimated lumen diameter) are expressed in square millimeters. The measurements were performed by 2 independent observers who were blinded as to the group to which the individual belonged. For each patient, optimal radial artery images were obtained between 2 and 5 cm above the radial styloid. This location was marked, and all subsequent images were obtained at the same location. In our study, the interobserver variability for the repeated measurements of resting radial artery diameter was 0.04 ± 0.02 mm. The intraobserver variability for the repeated measurements of resting radial artery diameter was 0.03 ± 0.02 mm.

Statistical Methods

Both the case-control and randomized studies were designed to have 80% power ($\beta = .20$) to detect a difference of 20% between the compared groups at an α value of .05, assuming that the SD of the percentage changes in the artery lumen surface seen at 2 hours would be approximately 15%. With these assumptions, we estimated that 15 subjects per group would be needed.

Comparisons of groups were performed with the t test and nonparametric Mann-Whitney U test for continuous variables and the Fisher exact test for discrete variables, as appropriate. Pre-post comparisons with paired observations were analyzed by using the Wilcoxon test. Linear regression models were built with least-squares methods by using all variables and also with a backward elimination approach, starting with all variables that were significant ($P < .05$) in univariate relationships and eliminating variables with P values of greater than .05 in a stepwise fashion. Given the limited sample size, multivariate models should be viewed cautiously, but they are useful in further validating the unadjusted results. All analyses were conducted with SPSS 10.0 software (SPSS Inc, Chicago, Ill), and all P values are 2-tailed.

Results

Characteristics of Subjects

Tables 1 and 2 summarize key characteristics of the subjects in the case-control study and of the patients in the randomized controlled trial. As shown, there were no significant differences between the compared groups for either of the 2 comparisons. High cholesterol, diabetes, and hypertension were relatively common among the preoperative patients with coronary artery disease who were enrolled in the randomized trial. Left ventricular ejection fractions were similar, and the use of β -blockade was not different in the 2 groups.

Case-control Study: Evaluation of Vitamin C in Smokers Versus Nonsmokers

Both smokers and nonsmokers showed a statistically significant increase in the radial artery lumen surface at 2 hours compared with at baseline ($P < .001$ and $P = .013$, respectively, Wilcoxon test). Nonsmokers showed a median increase of 14.3% (interquartile range [IQR], 0%-28.6%; mean, 16.0%), whereas the respective increase in smokers was 37.5% (IQR, 25.0%-57.1%; mean, 42.4%). The increase in the lumen surface was significantly larger in the group of smokers (Figure 2). After adjusting for age in a

Figure 1. High-resolution ultrasound and color Doppler images in a preoperative patient with coronary artery disease before (*right images*, lumen surface of the radial artery, 10 mm²) and 2 hours after the oral administration of 2 g of vitamin C (*left images*, lumen surface of the radial artery, 14 mm²).

TABLE 1. Summary of the key characteristics of the subjects in the case-control study

	Case-control comparison in healthy adults		P value
	Nonsmokers	Smokers	
Age, median (IQR)	29 (25-34)	31 (29-46)	.17
Male/female sex	9/6	8/7	.46
History of smoking	0	15	—
High cholesterol	0	0	—
Diabetes mellitus	0	0	—
Diastolic blood pressure, mean (SD)	Normal	Normal	—
Systolic blood pressure, mean (SD)	Normal	Normal	—
Baseline surface in mm ² , median (IQR)	9 (8-13)	9 (8-10)	.13

multivariate model, smokers still had a larger increase (+30.4%, $P = .0016$), whereas age had a marginal influence, with decreasing response in older subjects (-0.60% per year, $P = .092$).

Randomized Study of Vitamin C Versus Diltiazem

Both patients in the vitamin C group and patients in the diltiazem group showed statistically significant increases of

the radial artery lumen surface at 2 hours compared with baseline values ($P < .001$ and $P = .008$, respectively, Wilcoxon test). Patients receiving vitamin C showed a median increase of 33.3% (IQR, 14.3%-45.5%; mean, 35.4%), whereas the respective median increase in the diltiazem group was only 18.2% (IQR, 0%-22.2%; mean, 16.9%). The difference was statistically significant (Figure 3).

In an adjusted analysis considering age, sex, systolic and

Figure 2. Baseline and 2-hour values of radial artery surface area in smokers and nonsmokers. Given a similar baseline value, smokers typically achieve larger vasodilatation at 2 hours ($P = .005$ by t test and $P = .004$, Mann-Whitney U test). Not shown is one outlier in the nonsmoker group. The regression lines are fit separately to each group (2-hour value = $2.9 + 0.86 \times$ baseline value for the nonsmokers and $7.9 + 0.50 \times$ baseline value for smokers).

Figure 3. Baseline and 2-hour values of radial artery surface area in the diltiazem and vitamin C groups. Given a similar baseline value, patients receiving vitamin C typically achieve larger vasodilatation at 2 hours ($P = .043$ by t test and $P = .016$, Mann-Whitney U test). The regression lines are fit separately to each group (2-hour value = $1.0 + 1.25 \times$ baseline value for the vitamin C group and $3.7 + 0.78 \times$ baseline value for the diltiazem group).

TABLE 2. Summary of the key characteristics of the patients in the randomized controlled study

	Randomized study in patients with CAD		P value
	Vitamin C	Diltiazem	
Age, median (IQR)	72 (67-74)	69 (65-73)	.27
Male/female sex	10/5	9/6	.71
History of smoking	10	8	.46
High cholesterol	7	9	.47
Diabetes mellitus	5	7	.46
Diastolic blood pressure, mean (SD)	86 (7)	89 (8)	.29
Systolic blood pressure, mean (SD)	141 (17)	149 (19)	.25
Baseline surface in mm ² , median (IQR)	9 (8-11)	10 (9-12)	.30
Left ventricular ejection fraction (%), mean (SD)	50 (13)	52 (11)	.50
No. of diseased coronary arteries (median)	2	2	1.00
Use of β blockade (no. of patients)	4	5	.70
Use of nitrates	0	0	1.00
Use of angiotensin-converting enzyme inhibitors	7	8	.72
Use of calcium-channel blockers	0	0	1.00

CAD, Coronary artery disease.

diastolic pressure, the presence of diabetes mellitus, high cholesterol levels, and history of smoking, vitamin C still resulted in a statistically better response than diltiazem (+22.4%, $P = .009$). A backward elimination model starting from these variables showed that the percentage response was independently predicted by the use of vitamin C over diltiazem (+21.2%, $P = .007$), diabetes mellitus (+14.5%, $P = .085$), high cholesterol levels (+26.2%, $P = .001$), and a history of smoking (+20.8%, $P = .017$). Age,

sex, and blood pressure were not retained as independent predictors in this multivariate model. There was no strong evidence of interaction effects between the retained independent predictors.

Safety

There were 2 patients with asymptomatic modest decreases in blood pressure and heart rate in the diltiazem group. No other side effects were observed.

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Discussion

The vasodilator of choice in radial conduits is still a matter of controversy.²²⁻²⁵ Neurohormonal activation during coronary revascularization stimulates the release of bioactive peptides and catecholamines, both of which might contribute to early radial artery vasospasm.²² Endothelin and nor-epinephrine cause vascular smooth muscle contraction through the activation of calcium channels.²² This engages the contractile apparatus, resulting in vasoconstriction.

Calcium-channel antagonists are selective vasodilators that inhibit the voltage-dependent calcium channel in human arteries;²³ they are less effective at inhibiting vascular contraction mediated by receptor mechanisms.²³

Diltiazem is a 1,5-benzothiazepine that binds to the α_{1C} subunit of the L-type calcium channel, the main pore-forming unit of the channel.²⁵ Blockage of L-type calcium channels in vascular tissues results in relaxation of vascular smooth muscle and vasodilation.²⁵ L-Type blockade in the heart, however, results in negative inotropic and chronotropic effect that induces bradycardia, particularly when used in combination with β -blockers,²³ a cornerstone in the management of ischemic heart failure. It is also notorious for the frequent need to modify its dosage or discontinue its administration because of hypotension perioperatively. Moreover, use of diltiazem does not completely eliminate spasm and has been reported to be less effective than other vasodilators, such as nitroglycerin.^{24,25}

Vitamin C (ascorbate), an antioxidant factor, improves defective endothelial function. This has been attributed to an enhancement of the synthesis or prevention of the breakdown of nitric oxide.²¹ Vitamin C–induced decreases in low-density lipoprotein oxidation, scavenging of intracellular superoxide, release of nitric oxide from circulating or tissue S-nitrosothiols, direct reduction of nitride to nitric oxide, and activation of either endothelial nitric oxide synthetase or smooth muscle guanylate cyclase might all be implicated in the ability of ascorbate to preserve nitric oxide.^{21,26,27}

Smoking has a direct toxic effect on human endothelial cells.¹⁴ The gas phase of cigarette smoke contains free radicals and pro-oxidants, and the particulate phase contains high concentrations of lipophilic quinones, which can form the highly reactive OH[•] radical.¹⁴ In addition, superoxide anion, which directly originates from smoke, results in the formation of peroxynitrite anion (ONOO[−]), which reduces the vasoactive level of nitric oxide.¹⁴ In our case-control study vitamin C was able to achieve substantial vasodilation of the radial artery among healthy young adults, and the effect was more prominent among smokers. This suggests that vitamin C might be even more useful among smokers, in whom the underlying vasoconstrictive effects might be more prominent, and the mechanism of action of vitamin C might share a common pathway counterbalancing the bio-

logic effects of chronic smoking. Interestingly, smokers are known to have lower plasma²⁸ and tissue¹⁵ vitamin C levels than nonsmokers.

Vitamin C has a potent acute vasodilating effect on the radial artery, and the effect is more prominent among smokers. On the basis of this (first to our knowledge) double-blind randomized comparison, we demonstrated that a single oral dose of vitamin C achieves better vasodilation of the radial artery than diltiazem in preoperative coronary patients. In the multivariate analysis of the data from the randomized trial, vitamin C was superior to diltiazem in achieving radial artery vasodilation, even when all the other key risk factors that seem to affect endothelial dysfunction (including smoking, hypertension, diabetes, and hypercholesterolemia) were taken into account.

Study Limitations

The beneficial effects of vitamin C might not necessarily translate into efficacy during the perioperative manipulations after an acute surgical, metabolic, and pharmacologic assault. Furthermore, in healthy young smokers vitamin C has been shown not to have sustainable, long-term effects on endothelial function, despite sustained increase of plasma ascorbate levels,²⁰ and although vitamin C improves endothelial dysfunction, there is no proved relationship between baseline ascorbic acid concentration and baseline endothelial function.¹² Our results, however, suggest a potential role for this substance in the management of patients receiving radial artery grafts. This role would have to be further delineated against other available vasodilation options in this setting. For example, in addition to calcium-channel blockers, nitroglycerin has also shown significant efficacy for preventing coronary bypass conduit spasm,^{24,25} and a combination of calcium-channel blockers with nitroglycerin²⁹ might be even more potent. However, recent evidence of unchanged coronary vascular resistance during postoperative nitroglycerin administration casts doubt on such use.³⁰ Future studies should compare vitamin C against such combinations.

Conclusion

The results of the present study provide evidence that vitamin C is a potent vasodilator in healthy subjects, particularly smokers. In addition, it is a superior acute vasodilating agent in vivo compared with diltiazem in ischemic patients awaiting cardiac surgery. This pilot study should justify a perioperative trial to evaluate the vasodilating effect of vitamin C on radial artery conduits during coronary revascularization.

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