Effect of Chelation Therapy on Endothelial Function in Patients With Coronary Artery Disease: PATCH Substudy

Todd J. Anderson, MD, FRCP(C), Jaroslav Hubacek, MD, MSc, D. George Wyse, MD, PhD, FRCP(C), Merrill L. Knudston, MD, FRCP(C)

Calgary, Canada

OBJECTIVES

The purpose of this study was to evaluate the effect of chelation therapy with ethylenediamine tetraacetic acid (EDTA) on endothelium-dependent vasomotor responses in patients with documented coronary artery disease (CAD).

BACKGROUND

Oxidative stress plays an important role in the dysfunction of endothelium and development of atherosclerosis. Modification of cardiac risk factors and employment of antioxidants have been shown to improve endothelial function. Ethylenediamine tetraacetic acid chelation therapy is considered to be a complementary therapy for patients with CAD and is proposed to have antioxidant properties.

METHODS

A total of 47 patients enrolled in the Program to Assess Alternative Treatment Strategies to Achieve Cardiac Health (PATCH) participated in this substudy and had complete data. High-resolution ultrasound was used to assess endothelium-dependent brachial artery flow-mediated vasodilation (FMD) in patients with CAD in a randomized, double-blind, and placebo-controlled fashion. Patients were randomized to chelation therapy or placebo. The primary end point was the absolute difference in FMD after the first and 33rd treatments (6 months) of study groups compared with their baselines.

RESULTS

At the baseline, the study population had mild impairment of FMD (7.2 ± 3.4%). The first chelation treatment did not change FMD as compared with placebo (chelation 6.5 ± 3.5% vs. placebo 7.4 ± 2.9%; p value = 0.371). The brachial artery studies at six months did not demonstrate significant differences in FMD between study groups (placebo 7.3 ± 3.4% vs. chelation 7.3 ± 3.2%; p value = 0.961).

CONCLUSIONS

Our results suggest that EDTA chelation therapy in combination with vitamins and minerals does not provide additional benefits on abnormal vasomotor responses in patients with CAD optimally treated with proven therapies for atherosclerotic risk factors. (J Am Coll Cardiol 2003;41:420–5) © 2003 by the American College of Cardiology Foundation

Chelation therapy or intravenous infusion of ethylenediamine tetraacetic acid (EDTA) in combination with oral vitamins and minerals is considered an “alternative” or “complementary” therapy for patients with coronary artery disease (CAD). It has been suggested that patients with CAD might benefit from this complementary therapeutic approach (1–4). However, definitive evidence that chelation is beneficial has been lacking in randomized trials. Several mechanisms for the potential beneficial effects of chelation therapy in patients with atherosclerosis have been postulated. Lamas and Ackermann (5) suggested that an antioxidant effect of EDTA, in combination with vitamins and minerals, might be the most plausible.

Over the past decade, emerging data have demonstrated that cardiovascular risk factors and oxidative stress play a crucial role in abnormal vasomotor responses (6). Abnormal vasomotor responses are probably one of the first events in the atherosclerosis process and have been shown to be an important cause of ischemia in patients with established atherosclerosis (7). Furthermore, modification of cardiac risk factors and employment of antioxidants have been shown to improve endothelial function (8). On the basis of previously proposed antioxidant, antihypertensive, and cholesterol-lowering properties of chelation therapy (9), we hypothesized that EDTA in combination with vitamins and minerals may have a beneficial effect on endothelial function in patients with established CAD.

The purpose of this study was to evaluate the effect of chelation therapy with EDTA on endothelium-dependent vasomotor responses in patients with documented CAD in a randomized, double-blind, and placebo-controlled fashion.

METHODS

Study subjects. A total of 53 patients enrolled in the Program to Assess Alternative Treatment Strategies to Achieve Cardiac Health (PATCH) study participated in this substudy. The main PATCH study has been previously reported (10). Briefly, patients ≥21 years old with CAD proven by coronary angiography or a documented myocardial infarction and stable angina on optimal medical therapy were studied. To qualify for randomization, patients were
required to have a treadmill test using a gradual ramping protocol and demonstrating ≥1 mm horizontal or downsloping ST depression from the isoelectric line 80 ms after the J point. The study required detection of ST depression between 2 and 14 min from the onset of exercise. Patients were excluded for the following reasons: planned revascularization, previous chelation therapy, evidence of heart failure, inability to walk on the treadmill, resting electrocardiogram changes that would interfere with ischemic assessment, abnormal renal or liver function, or untreated lipid abnormality at the time of randomization.

Study protocol. RANDOMIZATION AND TREATMENT. Written informed consent was obtained from all participants. The Conjoint Ethics Committee of the University of Calgary and the Calgary Regional Health Authority approved this study and its consent form. All clinical events were reported to an independent Safety Monitoring Committee. The present study was a double-blind, randomized, placebo-controlled trial. Patients were randomized in blocks of 10 using S-plus version 3.4 (Statistical Science and placebo-controlled trial. The Pharmacy assigned the randomized therapy and prepared treatments. In accordance with the American College of Cardiology protocol, patients in both groups took oral multivitamin therapy (FLW, Douglas Labs, Pittsburgh, Pennsylvania), two tablets three times daily as tolerated, except on treatment days. The components of FLW were as follows: vitamin A 4,000 IU, vitamin E 65 IU, vitamin C 400 mg, vitamin B1 20 mg, vitamin B2 5 mg, vitamin B6 15 mg, vitamin B12 25 µg, niacin 5 mg, niacinamide 5 mg, pantothentic acid 50 mg, folic acid 0.04 mg, biotin 10 µg, choline 72.5 mg, inositol 5 mg, methionine 24 mg, magnesium 40 mg, potassium 40 mg, manganese 0.5 mg, zinc 3 mg, chromium 20 µg, and selenium 25 µg. All patients were seen at the University of Calgary Cardiovascular Risk Reduction Clinic and had treatment of their risk profile optimized.

BRACHIAL ENDOTHELIAL FUNCTION STUDIES. A recently described technique employing high-resolution ultrasound to measure brachial artery diameter was used to study the vasodilator responses induced by reactive hyperemia after 5 min of upper arm occlusion (11). Assessment of brachial artery endothelial function was performed at baseline, after the first chelation therapy (acute), and at the end of study (after the completion of 33 chelation treatments) by a previously validated technique (12,13). Patients underwent each of three brachial artery ultrasound studies after an overnight fast (12 h), and all vasoactive medications, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers, long-acting nitrates, and statins were stopped for 24 h. Studies were performed in a quiet clinical laboratory with the temperature maintained at 21 to 23°C. A 7.5 MHz linear phase-arrayed ultrasound transducer attached to a Hewlett-Packard 5500 ultrasound machine was used. Pulsed-wave Doppler was used to record brachial artery velocity for each of the interventions.

Data analysis. BRACHIAL ARTERY ANALYSIS. Brachial artery analysis was performed at a core laboratory at the University of Calgary by a single technician blind to the study group assignment or study sequence. Three sequential systolic frames (taken at the end of the T-wave on the electrocardiogram) were digitized via an analog-to-digital converting board. A software algorithm automatically calculates the average diameter (100 points) over the operator-selected segment. Flow-mediated vasodilation (FMD) was calculated from the diameters as (reactive hyperemia − baseline)/baseline × 100%. The intra- and inter-observer variability in our laboratory is 1%. Systolic frames were used as previously validated (13). In 20 studies selected randomly, measurements were made at both end-diastole and systole, and the FMD was exactly the same. Brachial artery flow was calculated as the product of velocity and cross-sectional arterial area.

STATISTICS. Data are expressed as mean ± SD for continuous variables and as counts and percentage for discrete variables. Statistical analyses were conducted with a commercially available software package (SPSS version 10.0; SPSS Inc, Chicago, Illinois). The sample size was determined to detect a clinically important absolute improvement...
in FMD of 3% (with a SD of 3% to 4%) in the chelation group when compared with placebo. This assumes an alpha of 0.05 and beta 0.2. Categorical variables were analyzed with the Mann-Whitney U-test. Continuous variables were examined with paired and unpaired t tests, as appropriate. All reported significance levels are two-sided.

RESULTS

Patient characteristics. A total of 53 patients agreed and consented to participate in the study between January 1996 and January 2000. Of the 53 patients, 47 completed treatment and final brachial artery ultrasound study. Four placebo patients were unable to finish the treatment phase because of: 1) cancer of the hip; 2) hospitalization with pneumothorax in the setting of previous asbestosis and chronic obstructive pulmonary disease; 3) unstable angina followed by angioplasty and coronary artery bypass graft surgery; and 4) coronary artery bypass graft surgery that had been planned as an elective procedure by the primary cardiologist after randomization without the knowledge of the investigators. Two EDTA patients were unable to complete the study: one because of a serum creatinine level increase above preset study limit (175 μmol/l) and the other because of hospitalization for unstable angina followed by withdrawal of consent. There was no difference in the demographics of these patients and those who completed the study. Data presented in this report are from the 47 patients with complete information. The baseline characteristics of the 47 randomized patients are shown in Table 1. There were no important differences at baseline between the two groups. The mean age of the study population was 68 ± 9 years, with 85% men. Risk factors were as follows: hypercholesterolemia 80%, hypertension 43%, and diabetes mellitus 10%. All patients had treatment of their risk profile optimized. Among all 47 patients, 95% were treated with aspirin, 80% with lipid-lowering therapies, 70% with beta-blockers, 34% with ACE inhibitors, and 30% with long-acting nitrates. The use of medication was comparable between the randomization groups. During the course of the study, there was no statistically significant difference in lipid profile or in blood pressure between the groups.

Treatment effect on brachial artery characteristics. Flow-mediated vasodilation was inversely related to baseline brachial artery diameter in this study (baseline 4.1 ± 0.7 mm vs. FMD diameter 4.3 ± 0.8 mm; p value <0.001) and in other studies (13–15). The baseline brachial artery diameter was the same for both study groups, and the study medications had no significant effect on baseline brachial artery diameter after six months of treatment. Upper arm occlusion resulted in an increase in forearm blood flow of approximately 450%, which was the same at baseline for both groups and was not affected by drug treatment.

Treatment effect on FMD. At the baseline, the study population had FMD of 7.2 ± 3.4% and nitroglycerin (NTG)-mediated dilation of 13.2 ± 5.7%. These values are similar to what we have reported previously in patients with CAD (14) and less than those of normal controls in our lab (16). Baseline FMD and NTG-mediated vasodilations were similar in both groups (Table 2). Short-term treatment with EDTA in combination with vitamins and minerals did not change FMD and NTG-mediated vasodilation (Table 2). The brachial artery studies at six months, after the completion of 33 treatments, did not demonstrate significant differences in FMD between placebo and chelation therapy groups (placebo 7.3 ± 3.4% vs. chelation 7.3 ± 3.2%; p value = 0.961) (Table 2). There was no significant effect of chelation therapy on NTG-induced vasodilation (placebo 12.4 ± 6.4% vs. chelation group 15.3 ± 7.1%; p value = 0.148) (Table 2). Furthermore, we did not observe any statistically significant changes within either study group over time (Fig. 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographics</th>
<th>Placebo (n = 23)</th>
<th>Chelation (n = 24)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>64 ± 9</td>
<td>64 ± 9</td>
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<tr>
<td>Male</td>
<td>19 (83%)</td>
<td>21 (89%)</td>
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<tr>
<td>Female</td>
<td>4 (17%)</td>
<td>3 (13%)</td>
<td>0.641</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>4 (17%)</td>
<td>3 (13%)</td>
<td>0.641</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1 (4%)</td>
<td>4 (17%)</td>
<td>0.176</td>
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<tr>
<td>Hypertension</td>
<td>11 (48%)</td>
<td>9 (38%)</td>
<td>0.479</td>
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<tr>
<td>Smoker</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0.976</td>
</tr>
<tr>
<td>CHF</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0.976</td>
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<tr>
<td>PVD</td>
<td>3 (13%)</td>
<td>2 (8%)</td>
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<td>Lipids (mmol/l)</td>
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<td>Total cholesterol</td>
<td>5.0 ± 1.1</td>
<td>4.9 ± 0.8</td>
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<tr>
<td>LDL-C</td>
<td>3.0 ± 0.7</td>
<td>2.9 ± 0.7</td>
<td>0.639*</td>
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<tr>
<td>HDL-C</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>0.975*</td>
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<tr>
<td>Triglycerides</td>
<td>2.0 ± 1.1</td>
<td>2.8 ± 3.9</td>
<td>0.356*</td>
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<table>
<thead>
<tr>
<th>Table 2. Brachial Artery Parameters</th>
<th>Placebo</th>
<th>Chelation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline diameter (mm)</td>
<td>4.1 ± 0.7</td>
<td>4.0 ± 0.8</td>
<td>0.974</td>
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<tr>
<td>FMD (%)</td>
<td>7.6 ± 3.4</td>
<td>6.7 ± 3.5</td>
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<tr>
<td>NTG (%)</td>
<td>12.8 ± 5.0</td>
<td>13.5 ± 6.3</td>
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<td>Short-term</td>
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<tr>
<td>Baseline diameter (mm)</td>
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<td>4.1 ± 0.7</td>
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<tr>
<td>FMD (%)</td>
<td>7.4 ± 2.9</td>
<td>6.5 ± 3.5</td>
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<tr>
<td>NTG (%)</td>
<td>12.0 ± 4.9</td>
<td>12.8 ± 4.1</td>
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<td>6-month</td>
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<tr>
<td>Baseline diameter (mm)</td>
<td>4.1 ± 0.5</td>
<td>4.0 ± 0.8</td>
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<tr>
<td>FMD (%)</td>
<td>7.3 ± 3.4</td>
<td>7.3 ± 3.2</td>
<td>0.961</td>
</tr>
<tr>
<td>NTG (%)</td>
<td>12.4 ± 6.4</td>
<td>15.3 ± 7.1</td>
<td>0.148</td>
</tr>
</tbody>
</table>

**CHF** = history of congestive heart failure; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **p value** = chelation therapy versus placebo group; **unpaired t test and Mann-Whitney U-test** (*); **PVD** = peripheral vascular disease.
DISCUSSION

This randomized, double-blind, and placebo-controlled study demonstrates that short- and long-term treatment (33 infusions) with EDTA in combination with vitamins and minerals did not improve impaired endothelium-dependent FMD in the brachial artery circulation of patients with established CAD and optimized treatment of risk profile.

There is ample evidence that the endothelium plays an important role in maintaining vascular integrity through the release of a variety of paracrine and autocrine factors, including nitric oxide (NO). In health, NO causes vasodilation, inhibits platelet aggregation and adhesion, and inhibits smooth muscle cell proliferation and white cell adhesion (17). Endothelial dysfunction has been observed in patients with established CAD or coronary risk factors, both in coronary and peripheral circulation (12,18). Oxygen free radicals, generated by a number of pathways in the body, play an important role in the dysfunction of endothelium and development of atherosclerosis (19). Modification of cardiac risk factors and employment of antioxidants have been shown to improve endothelial function (8).

Chelation therapy is considered to be complementary therapy for patients with CAD. In fact, the beneficial effect of EDTA therapy in this setting remains unproven (5,10). Originally, liberation of plaque calcium with a subsequent favorable change in the properties of the plaque (20–23) was thought to be the underlying mechanism of action. Later, EDTA was proposed to lower low-density lipoprotein and very-low-density lipoprotein levels and iron stores, inhibit platelet aggregation, relax vascular tone, and “scavenge” free radicals,
radicals (5,20–29). Ethylenediamine tetraacetic acid reduces iron and copper levels from cell membrane. Both these metals are important catalysts in the peroxidation of unsaturated fatty acids and the oxidation of low-density lipoprotein, which generate free radicals with subsequent disruption of membrane architecture, promoting cellular injury and progression of atherosclerosis (30). The beneficial effect of iron chelation on endothelial function has been previously demonstrated. Deferoxamine, an iron chelator, improved NO-mediated, endothelium-dependent vasodilation in patients with CAD (31) and in diabetics with angiographically normal coronary arteries (32). On the other hand, in a non-randomized and non-blinded study (33), EDTA alone did not significantly improve either endothelium or NO-dependent vasodilation in patients with CAD after 10 chelation infusions over 60 days. However, EDTA in combination with predominantly B vitamins improved vasomotor responses and was associated with a significant reduction in homocysteine levels. The patients in our study had documented CAD and impaired endothelial function in peripheral circulation at baseline. An improvement in abnormal vasomotor responses has not been observed in patients randomized to EDTA therapy compared with patients randomized to placebo, either in the short term or at six months. Furthermore, we have not demonstrated any statistically significant changes in FMD or NTG-mediated vasodilation within the study groups over time. One possible explanation might be that EDTA, unlike deferoxamine, is too small to bind entire iron ions and it creates a seventh coordination site (34). As a result, iron remains in its catalytically active form, and EDTA–iron complex can catalyze the formation of the hydroxyl radical in a superoxide generating system (35).

In our study, “placebo treatment” contained a high dose of intravenous vitamin C and multivitamin oral supplementation. Therefore, we cannot exclude a beneficial effect of treatment with vitamins and minerals alone. Vitamin C is a water-soluble antioxidant that inhibits lipid peroxidation in vitro (36) and in vivo (37) by directly scavenging aqueous free radicals, by reducing the chain-carrying alpha-tocopherol radical, and by stabilization of tetrahydrobiopterin, which prevents uncoupling of eNOS (38,39). In clinical studies, vitamin C has been shown to reverse impaired endothelial function in patients with established CAD (40,41). However, long-term vitamin C supplementation did not show a consistent beneficial effect on the endothelial function of treated patients (42). The reason why our patient population, either in the EDTA or placebo group, did not respond to vitamin C treatment is not clear. All our patients were aggressively treated for atherosclerotic risk factors. The majority of our study population was treated with lipid-lowering therapy and 34% of patients used ACE inhibitors. Lipid-lowering therapies and ACE inhibition have been shown to augment endothelial NO synthesis, to inhibit endothelial superoxide anion in animal studies (43–46), and to have beneficial effects on abnormal vasomotor responses in humans (47–50). Therefore, it can be speculated that free radical production was suppressed below the level at which free radical scavengers used in the presented study (EDTA and vitamin C) could demonstrate their beneficial effect on vasomotor responses. It was a limitation of our study that we did not have a measure of oxidative stress or vitamin C levels.

In conclusion, our results suggest that chelation therapy with EDTA in combination with vitamins and minerals does not provide any additional benefit on abnormal vasomotor responses in patients with CAD optimally treated for atherosclerotic risk factors with proven therapies.

Reprint requests and correspondence: Dr. Todd J. Anderson, 1403 29th Street NW, Calgary, Alberta T2N 2T9, Canada. E-mail: todd.anderson@calgaryhealthregion.ca.

REFERENCES