Chelation Therapy for Ischemic Heart Disease
A Randomized Controlled Trial

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Context  Chelation therapy using EDTA is an unproven but widely used alternative therapy for ischemic heart disease.

Objective  To determine if current EDTA protocols have a favorable impact on exercise ischemia threshold and quality of life measures in patients with stable ischemic heart disease.


Setting  Participants were recruited from a cohort of cardiac catheterization patients and the practices of cardiologists in Calgary, Alberta.

Participants  We screened 3140 patients, performed a qualifying treadmill test in 171, and enrolled 84. Entry criteria included age at least 21 years with coronary artery disease proven by angiography or a documented myocardial infarction and stable angina while receiving optimal medical therapy. The required treadmill test used a gradual ramping protocol and patients had to demonstrate at least 1-mm ST depression.

Interventions  Patients were randomly assigned to receive infusion with either weight-adjusted (40 mg/kg) EDTA chelation therapy (n=41) or placebo (n=43) for 3 hours per treatment, twice weekly for 15 weeks and once per month for an additional 3 months. Patients in both groups took oral multivitamin therapy as well.

Main Outcome Measure  Change from baseline to 27-week follow-up in time to ischemia (1-mm ST depression).

Results  Thirty-nine patients in each group completed the 27-week protocol. One chelation patient had therapy discontinued for a transient rise in serum creatinine. The mean (SD) baseline exercise time to ischemia was 572 (172) and 589 (176) seconds in the placebo and chelation groups, respectively. The corresponding mean changes in time to ischemia at 27 weeks were 54 seconds (95% confidence interval [CI], 23-84 seconds; P<.001) and 63 seconds (95% CI, 29-95 seconds; P<.001), for a difference of 9 seconds (95% CI, −36 to 53 seconds; P=.69). Exercise capacity and quality of life scores improved by similar degrees in both groups.

Conclusion  Based on exercise time to ischemia, exercise capacity, and quality of life measurements, there is no evidence to support a beneficial effect of chelation therapy in patients with ischemic heart disease, stable angina, and a positive treadmill test for ischemia.

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not undergo catheterization and all other noncardiac patients who seek chelation therapy.

We undertook a randomized, double-blind, placebo-controlled clinical trial of chelation therapy using the American College for Advancement in Medicine (ACAM) protocol to determine the efficacy of EDTA with respect to exercise ischemia threshold, symptoms, and quality of life in patients with stable ischemic heart disease.

METHODS
Study Subjects
Patients were recruited from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) cohort of cardiac catheterization patients and the practices of community cardiologists in Calgary. Participants had to be aged 21 years or older and have coronary artery disease proven by coronary angiography or a documented myocardial infarction and stable angina while receiving optimal medical therapy. To qualify for randomization patients were required to have a treadmill test, using a gradual ramping protocol, demonstrating at least 1 mm of horizontal or downsloping ST-segment depression from the isoelectric line 80 milliseconds after the J point. The study protocol required detection of ST-segment depression between 2 and 14 minutes from the onset of exercise.

Exclusion criteria included planned revascularization, previous chelation therapy, evidence of heart failure, inability to walk on the treadmill, resting electrocardiographic (ECG) changes that would interfere with ischemic assessment, abnormal renal or liver function, or untreated lipid abnormality at the time of randomization.

Treadmill Testing
Treadmill testing was done at baseline and at 15 and 27 weeks after randomization. The protocol began with a level 1 treadmill test, slowly every 10 to 15 seconds, reaching an equivalent of 13 METs at 14 minutes. A 12-lead ECG was recorded every 20 seconds. Maximum oxygen consumption (\(\dot{V}O_2\)max) and anaerobic thresholds were determined by continuous measurement of expired gases using a gas analyzer (Medgraphics model CPX/D; MedGraphics Corporation, St Paul, Minn) calibrated online.

Randomization and Treatment
Patients were randomized in blocks of 10. Investigators were blinded to treatment assignment. The hospital pharmacy assigned the randomized therapy and prepared solutions for blinded administration of infusions. The 500-mL infusion solution of 5% dextrose in water for the active treatment containing disodium EDTA (Endrate; Abbott Laboratories, Abbott Park, Ill) was weight adjusted (40 mg/kg), with a maximum total dose for each treatment of 3 g. Each treatment solution also contained 750 mg of magnesium sulfate, 5 g of ascorbic acid, and 5 g of sodium bicarbonate (titrated to physiologic pH) in the 5% dextrose. Lidocaine, 80 mg, was added to relieve pain at the administration site. In the placebo infusion solution the EDTA was replaced by 20 mL of 0.9% sodium chloride. The infusion solutions were indistinguishable by color and labeling. The infusion solution was administered over 3 hours to minimize the potential unblinding effect of infusion-related adverse effects. All patients received treatments twice weekly for 15 weeks and once monthly for an additional 3 months, for a total of 33 treatments. In accordance with the ACAM protocol, patients in both groups took oral multivitamin therapy, 2 tablets 3 times daily as tolerated, except on treatment days. All patients were seen at the University of Calgary Cardiovascular Risk Reduction Clinic and had treatment of their risk profile optimized according to American Heart Association guidelines (including management of diet, lipid levels, angina, stress, and exercise).

Other Tests and Safety Monitoring
Dipstick urine testing was performed at each visit. Urinalysis and serum creatinine were measured at every fifth visit. Hematology, electrolyte, and cholesterol panels were measured at baseline and at 15 and 27 weeks. The study nurse supervised patients throughout the duration of therapy, and hourly pulse and blood pressure measurements were obtained.

Study End Points
Exercise parameters and quality of life questionnaires were collected at 15 and 27 weeks after randomization. The primary end point was the change in time to reach at least 1 mm of ST-segment depression at the 27-week evaluation. Patients who did not achieve ischemic changes at 27 weeks had the test period truncated at 14 minutes, and 14 minutes was recorded as their “time to ischemia.” Functional reserve was also measured by determination of \(\dot{V}O_2\)max and time to reach anaerobic threshold. Quality of life instruments included the Duke Activity Status Index, Health Status Survey Short Form-36, and Seattle Angina Questionnaire.

Follow-up and Clinical Events
All patients were followed up for 1 year from randomization. During this time, all clinical events were tabulated, including death, myocardial infarction, coronary artery bypass graft surgery, and percutaneous coronary intervention.

All patients signed an informed consent form. 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.

Statistical Analysis
A sample size of 40 per group was chosen to provide 90% power to detect a 60-second difference in mean change in exercise time from baseline to the 27-week follow-up, assuming an SD of 80 seconds within each group. The 60-second difference was based on a minimally important difference determined by a consensus of Calgary cardiologists. Statistical analysis was
performed using S-plus, version 6.0 (Mathsoft, Seattle, Wash). Categorical variables were analyzed with the χ² or Fisher exact test, as appropriate. Continuous variables were examined with paired and unpaired t tests. Graphical examination of the data showed that normal assumption was viable. All reported significance levels are 2-sided, and P<.05 was set as the significance level. All analyses of exercise and quality of life data were conducted using last-observation-carried forward.

RESULTS

Patients
A total of 3140 patients (Figure) were screened and 171 of these agreed to undergo a qualifying exercise test. Eighty-four patients met the treadmill test criteria, consented, and were randomized between January 1996 and January 2000. Baseline characteristics according to treatment assignment are shown in Table 1. There were no important differences between the groups. Of the 84 patients randomized, 78 completed treatment, the final treadmill test, and the final quality of life assessments (39 in each group). Four placebo patients and 2 chelation patients were unable to complete the treatment phase (Figure).

Exercise End Points
At baseline, mean (SD) treadmill test times to ischemic ECG changes were 572 (172) seconds in the placebo and 589 (176) seconds in the chelation groups. Both groups were able to significantly (P<.001) increase their exercise time to ischemia at the 27-week treadmill test (Table 2). Changes in exercise measurements of functional reserve (time to anaerobic threshold and \( V_{O2\text{max}} \)) are shown in Table 2. The magnitude of the increases in time to ischemic changes and to anaerobic threshold were not statistically different in the 2 groups. The increase in \( V_{O2\text{max}} \) was not significant at the 27-week treadmill test in the placebo group but the increase in the chelation group was significant (P=.03). However, the difference between these 2 results was not significant (P=.46).

Quality of Life
The changes in quality of life scores between baseline measurement and those obtained at the 27-week evaluation are shown in Table 2. There was a tendency for modest increases in quality of life scores in both groups with significant but similar improvements in the exertional capacity component of the Seattle Angina Questionnaire. Differences between the groups were not significant.

Ischemia and Other Clinical Events
Clinical events are presented on an intention-to-treat basis (all 84 patients included). The duration of follow-up was 1 year from randomization for each patient. There were no deaths during that time. One patient in the placebo group had a documented myocardial infarction and 6 other patients were admitted at least once for worsening angina. Four of these 7 patients had angioplasty and none had coronary artery bypass graft (CABG) surgery for these events, although 1 other patient had elective surgery (CABG was planned by the cardiologist after randomization without investigators’ knowledge). There was 1 myocardial infarction in the chelation group and 9 patients were admitted at least once for worsening angina. None of these had angioplasty or CABG surgery associated with these events.

One of the chelation patients was withdrawn from therapy because of an elevation in serum creatinine. During the first 10 treatments the patient’s serum creatinine level increased from 1.5 to 2.1 mg/dL (129 to 186 µmol/L, respectively). Treatment was stopped...
and the serum creatinine level decreased to 1.6 mg/dL (138 µmol/L) after 10 weeks. No other cause for the elevation in creatinine was found. In addition to the nonischemic events shown in the Figure leading to discontinuation of therapy, 3 additional placebo patients were hospitalized for nonischemic events: gout, lumbar back pain from a herniated disk, and gastrointestinal bleeding. These events did not interfere with completion of the treatment phase. There were no electrolyte results out of normal range during the study.

**COMMENT**

The main finding of this study was that chelation therapy had no beneficial effect on exercise time to ischemia, functional reserve for exercise, and quality of life in patients with proven ischemic heart disease, stable angina, and evidence of ischemia on treadmill examination. Accordingly, chelation therapy remains unproven in the treatment of ischemic heart disease.

EDTA is an amino acid complex with a high affinity for divalent and trivalent cations such as lead, magnesium, zinc, iron, and calcium. Conventional chelation therapy involves multiple infusions of EDTA to chelate lead, iron, copper, calcium, and other metal ions in a redox inactive state. Chelated metal ions are then excreted from the body in the urine. For this reason EDTA has been used as a chelating agent in clinical situations in which these elements are found in excess.16

Because calcium is often found in atheromatous plaques, early proponents hypothesized that EDTA might be effective in treating ischemic heart disease by liberating plaque calcium with a subsequent favorable change in the properties of the plaque.23-25 Oxidized cholesterol plays an important role in endothelial function and the formation of atherosclerotic plaque.25 There is at least some evidence, albeit controversial, that increased total body iron stores are associated with increased ischemic heart disease.23 Therefore, some of these hypotheses about chelation having a potential mechanism for benefit in ischemic heart disease have plausibility. In the absence of studies confirming such effects and, more importantly, confirming a definite clinical benefit of chelation therapy, it remains possible that anecdotal reported improvements are simply due to the spontaneous fluctuations in symptoms frequently seen in ischemic heart disease.24-27 In our trial, the 1-minute increase in exercise time to ischemia and the improvement in the exertional capacity component of the Seattle Angina Questionnaire in both groups is consistent with a combination of placebo24-27 and training effects28-30 commonly seen in studies of angina patients. Another potential explanation for improvement is that both

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**Table 1. Baseline Characteristics of Patients Completing Treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 43)</th>
<th>Chelation (n = 41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (8.5)</td>
<td>66 (9.1)</td>
<td>.86</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>32 (83.7)</td>
<td>33 (85.4)</td>
<td>.93</td>
</tr>
<tr>
<td>Creatinine, mean (SD), mg/dL</td>
<td>1.0 (0.20)</td>
<td>1.1 (0.23)</td>
<td>.19</td>
</tr>
<tr>
<td>Single vessel</td>
<td>17 (39.5)</td>
<td>21 (51.2)</td>
<td>.39</td>
</tr>
<tr>
<td>Multivessel</td>
<td>26 (60.5)</td>
<td>20 (48.8)</td>
<td>.62</td>
</tr>
<tr>
<td>CCS angina class, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>14 (32.6)</td>
<td>12 (29.3)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (39.5)</td>
<td>22 (53.7)</td>
<td>.53</td>
</tr>
<tr>
<td>II</td>
<td>9 (20.9)</td>
<td>5 (12.2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2 (4.7)</td>
<td>2 (4.9)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Previous cardiac events, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12 (27.9)</td>
<td>20 (48.8)</td>
<td>.08</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>19 (44.2)</td>
<td>19 (46.3)</td>
<td>.98</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>12 (27.9)</td>
<td>10 (24.4)</td>
<td>.91</td>
</tr>
<tr>
<td>Comorbid conditions, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (14.0)</td>
<td>7 (17.1)</td>
<td>.93</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (65.1)</td>
<td>23 (56.1)</td>
<td>.53</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>34 (79.1)</td>
<td>34 (82.9)</td>
<td>.86</td>
</tr>
<tr>
<td>Laboratory values, mean (SD), mg/dL†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>185 (34.7)</td>
<td>185 (30.9)</td>
<td>.77</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>43 (8.9)</td>
<td>45 (13.1)</td>
<td>.54</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>106 (27.0)</td>
<td>107 (22.4)</td>
<td>.97</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>177 (132.7)</td>
<td>177 (79.6)</td>
<td>.97</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 (0.20)</td>
<td>1.1 (0.23)</td>
<td>.19</td>
</tr>
<tr>
<td>Medication use, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>32 (74.4)</td>
<td>30 (73.2)</td>
<td>.90</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>23 (53.5)</td>
<td>19 (46.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Nitrates</td>
<td>19 (44.2)</td>
<td>10 (24.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Triple therapy‡</td>
<td>11 (25.6)</td>
<td>5 (12.2)</td>
<td>.12</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>13 (30.2)</td>
<td>11 (26.8)</td>
<td>.73</td>
</tr>
<tr>
<td>Aspirin</td>
<td>41 (95.3)</td>
<td>38 (92.7)</td>
<td>.61</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>37 (86.0)</td>
<td>28 (68.3)</td>
<td>.05</td>
</tr>
</tbody>
</table>

*CALC indicates coronary artery disease; CCS, Canadian Cardiovascular Society; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and ACE, angiotensin-converting enzyme. The CCS scale is measured from I to IV, with a higher score indicating greater severity.
†To convert cholesterol values to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.0113. To convert creatinine to µmol/L, multiply values by 88.4.
‡Triple therapy includes β-blockers, calcium channel blockers, and nitrates.
The document discusses Chelation Therapy for Ischemic Heart Disease. It mentions that patients with ischemic heart disease have been treated with optimal risk reduction therapy. Chelation therapy is practiced and promoted as a form of complementary or alternative medicine in many developed countries. Additional vitamins and mineral supplements are recommended for patients undergoing chelation therapy. In the study, both groups received multivitamins; we cannot exclude the possibility that these supplements could be partially responsible for the improvement that we saw in both groups.

In the literature, numerous authors have reported positive results in uncontrolled studies. Very few randomized clinical trials have been published on the effects of chelation therapy, and those that have been published were performed in patients with peripheral arterial disease. Olszewer et al published a small trial of 10 men with peripheral arterial disease in which improvement was demonstrated in walking distance after 20 treatments, but there were only 5 patients in each group and therapy was not blinded. Guldager and colleagues published a randomized, double-blind, placebo-controlled trial of 153 male patients with peripheral arterial disease (75 EDTA and 78 placebo), and during the 6-month follow-up no effect of EDTA on walking time or ankle-brachial blood pressure index was demonstrated. That trial has been criticized for the high dropout rate (123 completed 6-month follow-up).

van Rij et al published the results of a similar randomized, double-blind, placebo-controlled trial of walking time and ankle-brachial blood pressure indices in 32 patients (15 EDTA and 17 placebo) with claudication, which also showed no effect of EDTA therapy.

There is even less evidence in patients with ischemic heart disease. Kitchell et al conducted a placebo-controlled, double-blind, crossover study of 9 patients with coronary heart disease and assessed performance on a treadmill. The authors documented that 2 of 4 EDTA-treated patients benefited at 12 weeks but only 2 patients volunteered to be treated in the second phase, and neither patient showed improvement. No statistical analyses were presented in that study.

As with all randomized clinical trials, our results can be applied to fit only a similar population to that studied: patients with stable angina who are not candidates for revascularization and can exercise on a treadmill. Our study showed that following 33 treatments with EDTA therapy, there was no evidence of any benefit compared with placebo in either objective measurements of exercise capacity or in measurements of patient-perceived well-being. One patient receiving EDTA had a transient increase in serum creatinine. There was no difference in the number of clinical ischemic events, but our study was not powered to detect any such differences. According to our findings, the use of chelation therapy to increase ischemic threshold and improve quality of life cannot be supported for patients with ischemic heart disease. Larger trials with a broader range of patients will be needed to assess the safety and impact of EDTA therapy on clinical event rates.

Author Contributions: Study concept and design: Knudtson, Wyse, Galbraith, Brant, Hildebrand. Acquisition of data: Knudtson, Wyse, Galbraith, Hildebrand, Paterson, Richardson, Burkart, Burgess. Analysis and interpretation of data: Knudtson, Wyse, Galbraith, Brant, Burgess. Drafting of the manuscript: Knudtson, Wyse, Galbraith, Brant, Hildebrand, Paterson, Richardson, Burkart, Burgess. Critical revision of the manuscript for important intellectual content: Knudtson, Wyse, Galbraith, Brant, Hildebrand, Paterson, Richardson, Burkart. Statistical expertise: Wyse, Galbraith. Obtained funding: Knudtson, Wyse, Galbraith, Brant, Hildebrand. Administrative, technical, or material support: Knudtson, Wyse, Galbraith, Hildebrand, Paterson, Richardson, Burgess. Study supervision: Knudtson, Wyse, Galbraith, Paterson, Burkart, Burgess. Funding/Support: This study was supported by the Alberta Health Services Research and Innovation Fund, Medical Services Incorporated Research Foundation, and the Calgary Regional Health Authority.

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Table 2. Exercise Times, Oxygen Consumption, and Quality of Life Scores at Baseline and 27 Weeks*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo Group</th>
<th>Chelation Group</th>
<th>Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, Mean (SD)</td>
<td>Change, Mean (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Time to ischemia, s</td>
<td>572 (172)</td>
<td>626 (186)</td>
<td>54 (23 to 84)</td>
</tr>
<tr>
<td>Time to anaerobic threshold, s</td>
<td>555 (151)</td>
<td>571 (195)</td>
<td>16 (−27 to 59)</td>
</tr>
<tr>
<td>Vo2max, mL/min</td>
<td>1606 (484)</td>
<td>1646 (419)</td>
<td>40 (−53 to 134)</td>
</tr>
<tr>
<td>DASI</td>
<td>37.4 (13.4)</td>
<td>39.3 (14.5)</td>
<td>1.9 (−0.6 to 4.5)</td>
</tr>
<tr>
<td>SAQ exertion</td>
<td>64.8 (20.3)</td>
<td>73.2 (17.8)</td>
<td>8.3 (3.9 to 12.8)</td>
</tr>
<tr>
<td>SF-36 mental component summary</td>
<td>48.3 (10.4)</td>
<td>50.4 (9.2)</td>
<td>2.1 (−0.4 to 4.5)</td>
</tr>
<tr>
<td>SF-36 physical component summary</td>
<td>39.9 (11.0)</td>
<td>44.9 (10.7)</td>
<td>5.0 (2.7 to 7.3)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval. Maximum score on the Duke Activity Status Index (DASI) is 58.2, with a higher score indicating better physiologic reserve. Scores on the Seattle Angina Questionnaire (SAQ) range from 1-100, with a higher score indicating better levels of functioning. Scores on the Short-Form 36 (SF-36) range from 0-100, with a higher score indicating better health-related quality of life. Mean change values were rounded.
REFERENCES
