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Review Article

Chelation therapy in the treatment of cardiovascular diseases

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Coronary artery disease;
Peripheral artery disease;
Intermittent claudication;
Cardiovascular disease prevention;
Cardiovascular disease treatment

OBJECTIVE: We examined the effect of chelation therapy on cardiovascular diseases (CVDs).

BACKGROUND: EDTA is a chelating agent that binds to metals including calcium and facilitates their excretion. Chelation with EDTA is recommended by some practitioners to treat CVD with the hypothesis that reducing calcium reduces atherosclerotic calcification of arteries. However, chelation therapy has not been approved by the Food and Drug Administration, and its effectiveness is unclear.

METHODS: We searched PubMed for English language articles addressing the effect of chelation therapy on CVD events. Articles pertinent to the topic were reviewed in detail.

RESULTS: We identified 128 articles addressing the therapeutic value of chelation therapy on CVD; 38 were reviewed in detail including 20 case series and 7 randomized controlled trials. Sixteen case series and 3 randomized controlled trials showed benefit with chelation. The Trial to Assess Chelation Therapy included 1708 post–myocardial infarction patients and demonstrated benefit with chelation therapy, but the Trial to Assess Chelation Therapy investigators concluded that their results did not support the routine use of chelation therapy for post–myocardial infarction patients.

CONCLUSIONS: The effectiveness of chelation therapy in reducing recurrent CVD events is unclear, but possible, and warrants additional, carefully designed clinical trials.

Introduction

Chelating agents are molecules that form stable bonds with metallic atoms, making them more stable, soluble and resistant to disassociation. EDTA is a chelating agent that binds to calcium, lead, iron, copper, and other metal ions forming soluble complexes and facilitating their urinary excretion.[1] Chelation therapy using EDTA has been used in patients with cardiovascular disease (CVD) on the theory that calcium chelation may stabilize or reduce atherosclerotic plaque containing calcium. Other putative beneficial effects in CVD include free radical scavenging,[2] reduction of total body iron,[3] cell membrane stabilization, arterial dilatation due to reduced calcium channel activity, improve arterial wall elasticity, increased production of nitric oxide,[1,4] and reduction in lead and cadmium levels.[5]

Chelation therapy is generally well tolerated; however, the most common side effect is a burning sensation at the site of administration. More serious and potentially fatal side effects occur rarely but include heart failure, hypotension, hypocalcemia, kidney damage, and bone marrow suppression. Hypocalcemia and death may occur particularly if the chelation therapy is infused too rapidly.[6]

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The use of EDTA chelation therapy to treat CVD and other diseases has increased 68% from 2002 to 2007 in the United States according to the 2008 National Health Interview and Nutrition Survey, and an estimated 111,000 individuals are treated yearly with this technique although it is not approved by the Food and Drug Administration.[6,7] However, the value of chelation therapy in CVD management is debated. We performed a systematic review to evaluate whether chelation therapy is beneficial for CVD.

Methods

We searched PubMed to identify studies evaluating the role of chelation therapy in CVD using the search words "EDTA," "chelation therapy," "cardiovascular diseases," "coronary artery disease," "peripheral artery disease," "intermittent claudication," "cardiovascular disease prevention," and "cardiovascular disease treatment," alone and in combination. We identified relevant articles by examining the abstracts and identified additional articles of interest from these articles' citations. We comprehensively reviewed the studies conducted on the effects of chelation therapy on CVD.

Results

We identified 128 articles addressing the therapeutic value of chelation therapy on CVD, 38 were reviewed in detail. These included 20 case series and 7 randomized controlled trials (RCTs) (Table 1).

The first case series[8] to our knowledge, included 20 subjects with angina pectoris, and reported improvement in angina frequency and in exercise tolerance for 19 of the subjects, and 8 increased their walking distance to angina.

The first-published double-blind study[9] included 10 men with claudication, who were randomized to receive 20 chelation treatments plus MgSO4, B complex, and vitamin C, or placebo chelation therapy plus placebo supplements. The investigators broke the code after 10 treatments because only some subjects were improving. Only subjects receiving chelation had improved. The authors measured exercise performance and ankle-brachial index (ABI) before and after treatment. The improvement ratios or the values after treatment or values before treatment after 10 treatments for the chelation and placebo groups, respectively, were 2.65 vs 1.1 for a walking test, 1.89 vs 1.02 for the Master Exercise Test, 2.10 vs 1.01 for a bicycle stress test, 0.89 vs 0.63 for resting ABI, and 0.78 vs 0.54 for exercise ABI. The investigators subsequently gave EDTA to all subjects for the remaining 10 treatments and found a mean improvement ratio of 2.93 and an ABI of 0.95 at rest and 0.88 after exercise in the group who received 20 chelation treatments vs a mean improvement ratio of 1.96 and an ABI of 0.86 at rest and 0.75 after exercise in the group who received 10 placebo and 10 chelation treatments.[9] The results are of limited value because of the small sample size[7] and the fact that both investigators and subjects were unblinded during the study and chelation therapy was ultimately given to all subjects.

Two randomized, double-blind trials[10,11] examined the effect of chelation in patients with claudication. The first[10] measured walking distance and ABI in 153 patients with claudication randomly assigned to chelation or placebo treatment. A subset of 30 subjects also had angiograms and transcutaneous oxygen concentrations measured.[11] None of these measurements demonstrated improvement with chelation. Another trial[12] randomized 32 patients with claudication to chelation (n = 15) or control (n = 17) for a total of 20 infusions. ABI and walking distance were measured after 10 infusions, at the completion of treatment, and at 3, 6, and12 months after treatment. Resting ABI was improved after 3 months, but there were no other difference in walking distance or postexercise ABIs between the 2 groups.[12]

The Program to Assess Alternative Treatment Strategies to Achieve Cardiac Health (PATCH) trial–assigned patients with diagnosed CAD to chelation (n = 41) or placebo (n = 43) therapy.[1] There was no difference in the exercise time to ischemia between the 2 groups after 27 weeks and 33 treatments. A substudy of PATCH measured endothelium-dependent brachial artery flow-mediated vasodilation in 23 chelation and 24 placebo-treated subjects at baseline, after the first chelation therapy and at the end of study (after 33 treatments) and found no difference at any time point in this parameter.[13]

The National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart Lung and Blood Institute (NHLBI) sponsored the Trial to Assess Chelation Therapy (TACT). TACT was the first large study designed to determine whether chelation therapy, with or without high dose vitamins and minerals, is useful in post–myocardial infarction (MI) patients. TACT randomly assigned 839 participants to chelation and 869 to placebo infusions. Patients aged ≥ 50 years were included if they had evidence of an MI ≥6 weeks before enrollment.[14] Patients were further assigned to 4 groups: chelation with oral vitamins and minerals, chelation with placebo vitamins and minerals, placebo infusion with vitamins and minerals, and placebo infusions with placebo vitamins and minerals.[5] Chelation therapy or placebo was administered as 40 intravenous infusions over 28 months. The first 30 infusions were administered weekly followed by 10 maintenance infusions every 2 to 8 weeks.

Of the 1708 participants, 311 (18%) were lost to follow-up, nearly all because of withdrawal of consent (289 patients). These withdrawals were also not equally distributed between the treatment groups as more patients withdrew from the placebo infusion group (n = 174) compared with the chelation group (n = 115).[15] Why this is so, is not clear, but it does raise the question of whether the investigators and patients were truly blind to study assignment. Also coronary revascularization and hospitalization