Does chelation therapy work for ischemic heart disease?

Anju Anand Michael F. Evans, MD, CCFP

Knudtson ML, Wyse GD, Galbraith PD, Brant R, Hildebrand K, Paterson D, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* **2002;287:481-6.**

Research question

For patients with stable ischemic heart disease, does chelation therapy using ethylenediaminetetraacetic acid (EDTA) have a favourable effect on the ischemic threshold during exercise and improve patients' quality of life?

Type of article and design

Double-blind, randomized controlled trial in an outpatient setting.

Relevance to family physicians

Cardiovascular disease is the leading cause of death in Canadian adults. In 1999, Statistics Canada reported 78 942 deaths due to cardiovascular disease. Inevitably, many patients seen in family practice have ischemic heart disease. In recent years, patients have been considering alternative medicine for treating daily ailments and ongoing health problems.[1,2] Among the alternative therapies available for ischemic heart disease is chelation.

Chelation therapy involves serial infusion of organic chemicals (eg, EDTA, an amino acid complex) that bind metals and thereby "cleanse" the blood. Proponents of chelation therapy believe that liberating calcium in atheromatous plaques will lead to better cardiac outcomes, but studies have not demonstrated this. Ernst[3] concluded that chelation therapy should now be considered obsolete. Yet a recent Canadian survey showed that 8% of patients who had undergone cardiac catheterization claimed to use chelation therapy.[1] The cost of chelation treatment is estimated at $4000. This has great implications because many patients are not able to afford such expensive treatment, and if it is proven ineffective, these patients can save their money.

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.

Overview of study and outcomes

This study enrolled patients from a cohort of cardiac catheterization patients and from community-based cardiology practices in Calgary. Exclusion criteria included planned revascularization, previous chelation therapy, evidence of heart failure, inability to perform treadmill testing, electrocardiographic changes at rest that would interfere with assessment of ischemic changes, untreated lipid abnormalities, and abnormal liver or renal function.

Inclusion criteria required patients to be older than 21, to have proven coronary artery disease (CAD) demonstrated by angiography or documented myocardial infarction (MI), and to have stable angina while taking optimal medical therapy. Patients were required to have a qualifying treadmill test demonstrating a 1-mm downsloping or horizontal ST-segment depression.

Eighty-four patients were enrolled in the study and randomly assigned to receive either placebo (n = 43) or weight-adjusted EDTA chelation therapy by infusion (n = 41). Average age was 65 in the placebo arm and 66 in the chelation arm. Most patients in both study arms were male; mean left ventricular ejection fraction (LVEF) was 58 in the placebo arm and 62 in the chelation arm. Similar numbers of patients in each group had comorbidities (diabetes mellitus, hypertension, hyperlipidemia), previous cardiac events, various degrees of CAD, similar patterns of medication use, and various cholesterol levels. The sample size (40) allowed 90% power for detecting a 60-second difference in mean change during exercise (from baseline to follow up).

Therapy consisted of a 3-hour treatment biweekly for 15 weeks and then monthly for 3 months for a total of 33 treatments. In addition to treatment, both groups were required to take oral multivitamins. Treadmill testing was repeated at 15 and 27 weeks after randomization; each time, exercise parameters and quality-of-life questionnaires were collected.

Ms Anand *is in her final year of medical school at the University of Toronto.* **Dr Evans** *practises in the Department of Family and Community Medicine at the Toronto Western Hospital, University Health Network, and teaches in the Department of Family and Community Medicine at the University of Toronto.*

The primary end point was change in time to achieve ST-segment depression of 1 mm from baseline to the 27-week follow up. Secondary end points included quality-of-life assessment and changes in functional reserve (measured by oxygen consumption per unit time and time to reach the anaerobic threshold). Duration of follow up for ischemia and other clinical events was 1 year from randomization for each patient.

Results

At baseline, mean time to ischemia was 572 (standard deviation [SD] 172) seconds in the placebo group and 589 (SD 176) seconds in the chelation group. Of the 39 patients in both groups completing the protocol, mean changes in time to ischemia at 27 weeks were 54 seconds (95% confidence interval [CI] 23-84 s, $P<.001$) and 63 seconds (95% CI 29-95 s, $P<.001$) in placebo and chelation groups, respectively. The difference of 9 seconds between the groups ($P=.69$) was not deemed clinically significant. Functional reserve increased notably ($P=.03$) in the chelation arm but not in the placebo arm ($P=.39$), but the difference was not statistically significant ($P=.46$).

Quality-of-life scores were significantly improved in the placebo arm, but not the chelation arm on the Seattle Angina Questionnaire ($P<.001$) and the physical component of the Short-Form 36 ($P<.001$). There were no significant changes on the Duke Activity Status Index or on the mental component of the Short-Form 36. Finally, the authors reported that during the 1-year follow up, patients from the placebo arm had seven cardiac events, including one MI and four exacerbations requiring coronary artery bypass grafting (CABG), and patients in the chelation arm had 10 cardiac exacerbations, including one MI and no CABGs. The only adverse effect of chelation was a transient elevation in one patient's creatinine levels.

Analysis of methodology

Randomization was intended to balance demographic and prognostic factors in the two groups. Follow up was 27 weeks for study end points and 1 year for adverse events. Data were analyzed on an intention-to-treat basis. Both groups were treated equally aside from the intervention, so it appears to be a valid study. The primary end point (time to ischemia during exercise), however, might be a surrogate because some evidence suggests that intravenous ascorbic acid and magnesium (given in the infusions to both groups) and multivitamins also have beneficial effects[4] and could account for the marked improvement in time to ischemia in both groups. Also, the primary end point might not correlate with patients' symptoms or with long-term risk of cardiac events. Hence, another end point, such as cardiac events, might have had more clinical relevance. Larger trials are needed to correlate this therapy with rates of clinical events.

Application to clinical practice

This study shows that, for a select population, chelation is not a useful adjunct to medical treatment. Generalizability of the study is limited, however, because some cardiac patients are unable to undergo treadmill testing. Also, the effects of the other substances in the chelation infusion are not clearly understood.[4] It is useful to note that quality-of-life scores were similar for both groups (in fact, some improvement was noted in the placebo arm). With more patients turning to alternative therapies, it is important to educate them, especially when placebo worked as well as a $4000 treatment! The effectiveness of chelation for other cardiac events warrants further study.

Bottom line

- Based on this study, for patients with known ischemic heart disease and stable angina (on optimal therapy), who are not candidates for revascularization and have positive results of treadmill testing for ischemia, chelation therapy has no benefit over placebo.
- At 1-year follow up for clinical events (eg, MI, CABG), there were no differences between placebo and chelation arms. This is reassuring, except that this trial did not have the power to detect such differences.
- The study was short, but chelation seems benign: only one patient had a transient increase in creatinine levels. The main side effect of chelation therapy is its effect on people's bank accounts ($4000 per treatment!).
- Given the cost and lack of efficacy, we should not recommend chelation therapy to patients. A larger, more inclusive study yielding similar results would confirm the decision not to recommend it.

References

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2. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States—prevalence, costs, and patterns of use. *N Engl J Med* 1993;328(4):246-52.
3. Ernst E. Chelation therapy for coronary heart disease: an overview of all clinical investigations. *Am Heart J* 2000;140:139-41.
4. Bell SA. Chelation therapy for patients with ischemic heart disease. *JAMA* 2002;287:2077-8.

Points saillants

- Selon cette étude, pour les patients souffrant d'une cardiopathie ischémique connue et d'une angine stable (suivant une thérapie optimale) chez qui la revascularisation n'est pas propice et qui ont des résultats positifs d'ischémie lors d'épreuves à l'effort, le traitement par chélation n'a pas d'avantage par rapport au placebo.
- Après une année de suivi des événements cliniques (par exemple infarctus du myocarde, pontage artorocoronarien), il n'y avait pas de différence entre les groupes au placebo et à la chélation. C'est rassurant, sauf que cette étude n'avait pas la capacité voulue pour détecter de telles distinctions.
- L'étude était courte mais la chélation semblait bénigne: seulement un patient a eu une augmentation transitoire des taux de créatinine. Les principaux effets secondaires indésirables du traitement par chélation étaient dans le compte de banque des personnes (4 000$ par traitement!).
- Compte tenu du coût et du manque d'efficacité, nous ne devrions pas recommander aux patients le traitement par chélation. Une étude de plus grande envergure et plus inclusive qui se traduirait par des résultats semblables confirmerait la décision de ne pas le recommander.