EDTA chelation therapy meets evidence-based medicine

According to World Health Organization estimates, 16.7 million people die of cardiovascular diseases each year.[1] By the year 2010, it is estimated that cardiovascular disease will become the leading cause of death in developing countries and by 2020 it will contribute to nearly 25 million deaths worldwide.[2,3] Although therapies including drugs, lifestyle modification and revascularisation procedures have been demonstrated in clinical trials to be beneficial, they are under-utilised. Paradoxically, in spite of the under-use of evidence-based therapies, patients actively seek complementary and alternative medicine (CAM) treatments. While many alternative therapies involve oral vitamin and mineral supplements that are unlikely to cause harm, chelation therapy is one of the most aggressive and intensive CAM modalities.

Chelation therapy

Chelation is derived from the Greek word 'chele' which denotes the claw of a crab or lobster. The 'claw' in chelation therapy is the synthetic amino acid disodium ethylenediaminetetraacetic acid (EDTA) that, when administered intravenously, binds ionic calcium, trace elements and other divalent cations and transports these bound components out of the body in the urine. EDTA chelation is typically administered as a mixture with antioxidant vitamins and other compounds, repeatedly over weeks to months. In addition, patients receiving chelation therapy from CAM practitioners will often take oral high-dose antioxidant vitamin and mineral supplements.

EDTA chelation was used originally for the treatment of lead poisoning; it was in this setting that it was noted that patients with established atherosclerotic disease had improvement in coronary artery disease (CAD) symptoms.[4] These clinical observations led to case reports of the benefit of EDTA in treating patients with atherosclerosis,[5] and practitioners proposed various mechanisms of action.

The best-known proposed mechanism evolved as the concurrence of atherosclerotic plaque and arterial calcification was noted. Proponents of EDTA chelation believed that vascular calcification might have a central role in the development of arterial insufficiency. Thus, the hypothesis was born that EDTA could be antiatherogenic by virtue of its calcium-chelating actions. This central role of decalcification of atherosclerotic plaques utilising EDTA chelation initially led to the consistent use of disodium EDTA, as calcium EDTA will not bind additional divalent cations. From a practical perspective, however, although atherosclerotic plaques are components of the arterial wall, these plaques may not be exposed to circulating EDTA. The elevated amounts of calcium in the urine noted after chelation therapy may originate from bones and blood, rather than selectively from plaques. Thus, the central mechanistic hypothesis that EDTA chelation selectively decalcifies atherosclerotic plaque has little supportive scientific evidence. Although the calcium hypothesis spurred the initial use of EDTA chelation for vascular disease, it has been the growing body of clinical experience, reported as case reports and case series, that has spurred the growth of this practice.

For example, Cranton reported that by 1993, there were more than 4,600 published articles supportive of chelation therapy.[6] Taken together, these studies suggest a significant beneficial effect of chelation therapy. However, there are no adequate control groups, there is a lack of consistent end points and follow-up is incomplete. A cautious interpretation leads to the conclusion that there is a suggestion of benefit without definitive evidence.

Randomised trials

Three small published randomised trials of EDTA chelation for patients with atherosclerotic vascular disease have measured clinically relevant end points. Guldager *et al.* enrolled 159 patients with intermittent claudication, excluding patients with diabetes, cardiac disease or renal insufficiency.[7] Patients were treated over five to nine weeks with 20 infusions along with vitamin supplementation and magnesium. There were no differences between groups in any parameter studied.

In the second trial, Van Rij enrolled 32 patients with angiographically confirmed peripheral vascular disease.[8] There were no significant differences reported in pain-free walking distance or total walking distance between groups. At three months, however, there was some improvement in resting ankle-brachial index in both legs in the chelation group, with a significant between-groups effect favouring chelation.

The third trial, the Program to Assess Alternative Treatment Strategies to Achieve Cardiac Health (PATCH) was a six-month randomised trial that measured exercise capacity in 84 patients with stable angina.[9] Patients were eligible to participate in the trial if they were over the age of 21, had proven CAD, stable angina pectoris, and ≥ 1 mm ST-segment

depression within 2–14 minutes on a gradually ramping treadmill test. Seventy-eight patients were randomised to receive either EDTA treatment or placebo; all patients received oral multivitamins. The active-treatment group received 30 weekly infusions of up to 3 g of EDTA as well as intravenous vitamins including 5 g of ascorbic acid. The placebo group received the same infusion components and schedule except that EDTA was omitted. Both groups increased their exercise times by approximately one minute, without a significant between-groups difference. Although a difference in exercise time was not detected, the investigators concluded that a trial of a far larger sample size was necessary to reach any definitive conclusions.

Thus, there are ample reports in the form of case studies and case series to support the benefits of EDTA chelation therapy. On the other hand, a small number of randomised trials enrolling an aggregate of fewer than 300 patients have had generally null results. If chelation therapy were non-invasive, free of cost and without the potential for side effects, a randomised trial would not be imperative. However, chelation therapy is a world-wide practice received by 66,000 patients yearly in the US alone; it can be expensive (up to $5,000 for a full course of 40 to 50 infusions), and it imposes a significant patient burden.[10]

Additionally, the potential exists for serious side effects. Indeed, adverse effects have never been evaluated in a large-scale controlled, randomised trial. Reported toxicities emerge from many case series and case reports whose interpretability is limited by their design, lack of standardised protocols and uniformity of patient entry criteria. Notwithstanding the disparate sources of data, the most important potential adverse event from administration of EDTA is renal toxicity. Other major potential toxicities of chelation therapy include hypocalcaemia leading to tetany, seizure and death; fluid overload, leading to heart failure; elevated liver function tests; and hypoglycaemia, in insulin-requiring patients with diabetes.

The potential for public benefit, counterweighed by the potential for public risk, is precisely why chelation therapy must be tested in a randomised trial.

Formal assessment

The Trial to Assess Chelation Therapy (TACT), funded by the National Institutes of Health (NIH) and National Center for Complementary and Alternative Medicine (NCCAM), is precisely the vehicle which will uncover, in an objective fashion, the actual risks and benefits of chelation therapy. TACT is designed as a randomised, double-blind, placebo-controlled 2 x 2 factorial designed trial. It will enrol 1,950 patients, 50 years of age or older with a prior myocardial infarction, to test the effects of 40 infusions of a standardised chelation solution commonly recommended by the American College for Advancement in Medicine, as well as the effects of high-dose oral antioxidant vitamin and mineral supplementation.

Specific aims for this trial will be to determine whether chelation and/or high-dose supplements in patients with coronary heart disease will reduce the incidence of clinical cardiovascular events and to determine if they have acceptable safety profiles. The primary end point of this trial is a composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation and hospitalisation for angina. Currently, nearly 900 patients have been enrolled, and over 25,000 infusions have been administered in nearly 100 US sites. The results of TACT will provide either a significant positive result or an informative negative result upon which rational clinical decision-making and health policy can be based.

Conflict of interest

None declared.

References

1. World Health Organization. World Health Report. 2003. Shaping the future. Geneva: WHO. 2003.
2. Chockalingam A & VI. *Impending global pandemic of cardiovascular diseases.* Barcelona: Prous Science, 1999.
3. World Health Organisation. www.who.int/ncd/cvd
4. Clarke CN, Clarke NE, Mosher RE. Treatment of angina pectoris with disodium ethylene diamine tetraacetic acid. *Am J Med Sci* 1956;**232**:654-66.
5. Clarke NE, Clarke CN, Mosher RE. The in vivo dissolution of metastatic calcium; an approach to atherosclerosis. *Am J Med Sci* 1955;**229**:142-9.
6. Cranton EM FJ. Current status of EDTA chelation therapy in occlusive arterial disease. *J Hol Med* 1982;**4**:103-04.
7. Guldager B, Brixen KT, Jorgensen SJ, Nielsen HK, Mosekilde L, Jelnes R. Effects of intravenous EDTA treatment on serum parathyroid hormone (1-84) and biochemical markers of bone turnover. *Dan Med Bull* 1993; **40**:627-30.
8. van Rij AM, Solomon C, Packer SG, Hopkins WG. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. *Circulation* 1994;**90**:1194-9.
9. Knudtson ML, Wyse DG, Galbraith PD *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* 2002;**287**: 481-6.
10. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;**343**:1-19.

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