Review Article

Role of EDTA chelation therapy in cardiovascular diseases

J. S. SHRIHARI, A. ROY, D. PRABHAKARAN, K. SRINATH REDDY

ABSTRACT

Chelation therapy is a widely practised mode of treatment for atherosclerotic cardiovascular diseases all over the world. However, evidence for the utility of this therapy is limited and conflicting. We did a systematic review of the literature. The reference listings of the articles, obtained from a Pubmed search using relevant keywords, were searched for additional related articles. Most of the evidence supporting the use of EDTA chelation therapy is from case reports, small series or uncontrolled, open-label clinical trials. The published randomized controlled trials include few patients and their results are of limited value. Uncontrolled studies have reported symptomatic improvements but the few controlled trials suggest that these benefits are due to a placebo effect. The available data do not support the use of chelation in cardiovascular diseases. This therapy should be used only in the context of a research trial including patients who have failed to respond to conventional treatment.

Natl Med J India 2006;19:24–6

INTRODUCTION

Chelation therapy is usually practised and promoted as a form of complementary or alternative medicine.[1] There are several case reports and series claiming that chelation with ethylene diamine tetra-acetic acid (EDTA) is curative for heart diseases. According to one such report in 1993, more than 500 000 patients in the USA alone received this form of treatment for atherosclerotic vascular disease.[2] Another report from Canada found that 8% of patients undergoing cardiac catheterization had undergone chelation therapy in the past.[3] Projections from this study would mean that more than 1 000 000 patients in the USA and several times that number of patients worldwide would have received chelation therapy. Considering the public interest and controversies related to the therapy, we did a systematic review of the scientific evidence on the effectiveness of EDTA chelation therapy in cardiovascular diseases.

Chelation is a chemical process in which a substance is used to bind molecules such as metals or minerals, and hold them tightly so that they can be removed from any organ system of the body.[4] Chelation therapy is commonly administered as repeated intravenous infusions of EDTA, usually in combination with vitamins, trace elements and iron supplements, as a treatment for diseases such as lead and heavy metal poisoning.[1] EDTA is a synthetic amino acid that binds and removes metals and minerals from the body. EDTA was first used in the 1940s for the treatment of heavy metal poisoning. EDTA chelation is approved and recommended for the extraction of heavy metals and minerals such as lead, iron, copper and calcium from the blood. Chelation therapy has been scientifically proven to be highly effective in treating lead poisoning and toxicity due to other heavy metals. Although it is not approved for the treatment of coronary artery disease (CAD), some physicians and alternative medicine practitioners recommend EDTA chelation to treat CAD.[1,4]

METHODS

We did a literature search using Pubmed to identify all relevant studies evaluating the role of chelation therapy in cardiovascular diseases. These articles were also used for collecting further articles from their reference listings. The internet search keywords used were 'chelation therapy, EDTA chelation therapy, chelation therapy and cardiovascular diseases, chelation therapy and ischaemic heart disease, cardiovascular diseases and coronary artery disease'. In addition, ongoing and unpublished trials were searched through *ClinicalTrials.gov*. After screening the studies, we reviewed 3 case reports, 2 uncontrolled studies and 7 randomized, double-blind, controlled studies.[1,4,5–11]

MECHANISM OF ACTION OF EDTA CHELATION THERAPY

The proponents of EDTA therapy claim that EDTA extracts calcium from arteriosclerotic plaques, de-blocks arteriosclerotic arteries and accelerates regression of plaques. According to the supporters of the therapy, EDTA is effective in reversing the arteriosclerotic disease process, specifically in patients with peripheral vascular disease who may require an amputation.[1]

Several theories have been suggested by the proponents of this form of treatment, but none of them have been tested scientifically. One theory claims that EDTA chelation might work by directly removing calcium found in fatty plaques that block the arteries, causing the plaques to break up. A second theory suggests that the process of chelation may stimulate the release of a hormone, which in turn causes calcium to be removed from the plaques or causes a lowering of cholesterol levels. A third suggests that EDTA chelation therapy may work by reducing the damaging effects of oxygen ions (oxidative stress) on the walls of the blood vessels.

All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

J. S. SHRIHARI, A. ROY, D. PRABHAKARAN, K. SRINATH REDDY
Department of Cardiology

Correspondence to D. PRABHAKARAN; *prabhakaran61@yahoo.com*

Reduction in oxidative stress could further reduce inflammation in the arteries and improve blood vessel function.[1]

In the early 1960s, an understanding of the mechanism of calcium chelation led to the hypothesis that EDTA could remove calcium that had been deposited in the arteries. Further, it was thought that once the calcium was removed by regular administration of EDTA, the remaining elements in the plaque would break up and the plaque would clear away, restoring the lumen of the narrowed arteries. Based on these assumptions, proponents of EDTA advocated its use in the treatment of existing atherosclerosis and to prevent further progression. Usually the therapy involves 5–30 sessions of treatment in the first month. This is often followed by preventive treatment once a month.[12]

SIDE-EFFECTS OF EDTA CHELATION THERAPY

When used for the treatment of heavy metal poisoning, chelation with EDTA has few side-effects. However, EDTA chelation therapy to treat CAD has been reported to be associated with severe, life-threatening adverse effects. These include hypotension, hypocalcaemia, headache, nausea, vomiting, hypoglycaemia, arrhythmias, tetany, prolonged bleeding time, convulsions, respiratory arrest, autoimmune diseases, bone marrow depression and injury to the kidneys.[4,5]

PUBLISHED EVIDENCE ON THE EFFECTS OF EDTA CHELATION THERAPY

Our review of the published studies shows insufficient evidence to support the safety and efficacy of EDTA chelation therapy for CAD. A large majority of evidence supporting the use of EDTA chelation therapy is in the form of case reports, case series and uncontrolled, open-labelled clinical trials. There are reports from patients who have undergone chelation therapy and physicians who prescribed it claiming improvement in CAD. Although each descriptive study reported reduction in angina, they were uncontrolled clinical observations or retrospective data, typically with a small number of participants. Further, the published randomized clinical trials involved few patients, making interpretation of the results difficult. A systematic Cochrane Data Review by Villarruz *et al.* analysed 5 studies (involving 260 patients in the study group) of chelation therapy and concluded that there was not enough evidence to support or negate the benefits of this therapy.[13]

We have summarized the details of 7 randomized, double-blind clinical trials (Table I). Among these, a study involving 41 participants in the EDTA group and 43 in the placebo group appears to be the best-designed trial of chelation therapy in CAD to date. This study reported that chelation therapy had no beneficial effect on exercise time to ischaemia, functional reserve for exercise, and quality-of-life in patients with proven ischaemic heart disease, stable angina and evidence of ischaemia on treadmill examination.[15] Another sub-study of this trial reported that chelation therapy does not provide any additional benefit in terms of improvement in endothelial function among patients optimally treated for atherosclerotic risk factors with proven therapies.[16]

Among the studies evaluating chelation therapy in patients with peripheral vascular disease, the design of three studies was good.[14,17–20] Guldager *et al.* in their randomized, double-blind, placebo-controlled trial of 153 men with peripheral arterial disease (75 EDTA and 78 placebo) did not find any beneficial effect of EDTA on walking time or ankle–brachial blood pressure index at 6 months of follow up.[19] van Rij *et al.* in a 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 did not find any beneficial effect of EDTA therapy either in patients with peripheral vascular or those with ischaemic heart disease.[20]

Sloth-Nielsen *et al.* in their multicenre study of 153 patients with peripheral vascular disease found no significant symptomatic or angiographic improvement in the EDTA group compared with the placebo group.[18] Olszewer *et al.* published a small trial of 10 men with peripheral arterial disease, in whom improvement in walking distance was demonstrated after 20 sessions, but there were only 5 patients in each group and the therapy was not blinded.[20]

While several uncontrolled investigations have reported symptomatic improvements, the few controlled trials suggest that these benefits are caused by placebo effects. Therefore, in view of its potential risks as well as poor scientific evidence, chelation therapy for CAD should be discarded in favour of therapies of proven efficacy.[21] A review by the American Heart Association's Clinical Science Committee on the use of chelation (EDTA) in the treatment of arteriosclerotic heart or blood vessel disease says, 'There is no scientific evidence to demonstrate any benefit of this form of therapy. Employment of this form of unproven treatment may deprive patients of the well established benefits attendant to the many other valuable methods of treating these diseases.'[12]

Recently, the National Institutes of Health (NIH) of USA has started a large multicentric, placebo-controlled, double-blind study called TACT (Trial to Assess Chelation Therapy) among 2372 participants aged >50 years with prior myocardial infarction to test whether EDTA chelation therapy and/or high-dose vitamin therapy is effective for the treatment of CAD. This study is reported to be over 20 times larger than any previous study of chelation therapy and large enough to detect if there are any mild or moderate benefits or risks associated with the therapy.[4] The results of this study are likely to provide conclusive evidence on the role of chelation therapy in CAD.

TABLE I. Details of the 7 randomized, double-blind, controlled clinical trials

Authors (Year)	Patient profile	Sample size	Randomization	Blinding	Results
Kitchell *et al.* 1963[14]	Coronary artery disease	28	Not described	Double; but not explained clearly	No benefits
Knudtson *et al.* 2002[15]	Coronary artery disease	84	Described	Double	No benefit
Anderson *et al.* 2003[16]	Coronary artery disease	53	Described	Double	No benefit
Olszewer *et al.* 1990[17]	Peripheral arterial disease	10	Not described	Double; initially double-blinded, but continued as single blind after 10 sessions	Improvement in walking distance
Sloth-Nielsen *et al.*1991[18]	Peripheral vascular disease	153	Not described	Double	No benefit
Guldager *et al.*1992[19]	Peripheral arterial disease	153	Described	Double	No benefit
van Rij *et al.* 1994[20]	Peripheral vascular and ischaemic heart disease	32	Described	Double	No benefit

CONCLUSION

The proponents of chelation therapy believe in pathophysiological models of arterioscleroiss, which appears too simplistic and discordant with the current state of knowledge.[1] Several clinical trials with outstanding methodological background have given convincing and definitive results, stating that in peripheral arterial occlusive disease, the short term as well as long term effects of EDTA chelation therapy do not ameliorate symptoms, nor do they change objective signs of the disease or subjective well-being to a greater extent than placebo treatment. Similarly, the available double-blind, randomized trials have reported that EDTA chelation therapy in combination with vitamins and minerals does not provide additional benefits in CAD. The large NIH-sponsored trial should probably provide the final word on this mode of therapy. Till the results of the NIH trial are available, this form of therapy for atherosclerotic vascular disease should be considered experimental and used only in the context of a research programme in patients in whom conventional treatments have failed and not as a definitive therapeutic modality.

REFERENCES

1 Ernst E. Chelation therapy for peripheral arterial occlusive disease: A systematic review. *Circulation* 1997;**96:**1031–3.

2 Babu AN, Gonzalez-Pena H. Iron chelating agents are not useful in treating atherosclerosis. *Ann Intern Med* 1994;**121:**384–5.

3 Quan H, Ghali WA, Verhoef MJ, Norris CM, Galbraith PD, Knudtson ML. Use of chelation therapy after coronary angiography. *Am J Med* 2001;**111:**686–91.

4 The NIH Trial of EDTA Chelation Therapy for Coronary Artery Disease. National Center for Complementary and Alternative Medicine, National Institutes of Health (NIH), USA. Available at *http://nccam.nih.gov/news/2002/chelation/q-and-a.htm#3* (accessed on 25 July 2005)

5 Ernst E. Chelation therapy for coronary heart disease: An overview of all clinical investigations. *Am Heart J* 2000;**140:**139–41.

6 Magee R. Chelation treatment of atherosclerosis. *Med J Aust* 1985;**142:**514–15.

7 McGillem MJ, Mancini GB. Inefficacy of EDTA chelation therapy for coronary atherosclerosis. *N Engl J Med* 1988;**318:**1618–19.

8 Grebe HB, Gregory PJ. Inhibition of warfarin anticoagulation associated with chelation therapy. *Pharmacotherapy* 2002;**22:**1067–9.

9 Wirebaugh SR, Geraets DR. Apparent failure of edetic acid chelation therapy for the treatment of coronary atherosclerosis. *DICP* 1990;**24:**22–5.

10 Green DJ, O'Driscoll JG, Maiorana A, Scrimgeour NB, Weerasooriya R, Taylor RR. Effects of chelation with EDTA and vitamin B therapy on nitric oxide-related endothelial vasodilator function. *Clin Exp Pharmacol Physiol* 1999;**26:**853–6.

11 Olszewer E, Carter JP. EDTA chelation therapy in chronic degenerative disease. *Med Hypotheses* 1988;**27:**41–9.

12 American Heart Association. Questions and answers about chelation therapy. Available at *http://www.americanheart.org/presenter.jhtml?identifier=3000843* (accessed on 25 July 2005)

13 Villarruz MV, Dans A, Tan F. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev* 2002;CD002785.

14 Kitchell JR, Palmon F Jr, Aytan N, Meltzer LE. The treatment of coronary artery disease with disodium EDTA. A reappraisal. *Am J Cardiol* 1963;**11:**501–6.

15 Knudtson ML, Wyse DG, 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.

16 Anderson TJ, Hubacek J, Wyse DG, Knudtson ML. Effect of chelation therapy on endothelial function in patients with coronary artery disease: PATCH substudy. *J Am Coll Cardiol* 2003;**41:**420–5.

17 Olszewer E, Sabbag FC, Carter JP. A pilot double-blind study of sodium–magnesium EDTA in peripheral vascular disease. *J Natl Med Assoc* 1990;**82:**173–7.

18 Sloth-Nielsen J, Guldager B, Mouritzen C, Lund EB, Egeblad M, Norregaard O, *et al*. Arteriographic findings in EDTA chelation therapy on peripheral arteriosclerosis. *Am J Surg* 1991;**162:**122–5.

19 Guldager B, Jelnes R, Jorgensen SJ, Nielsen JS, Klaerke A, Mogensen K, *et al*. EDTA treatment of intermittent claudication—A double-blind, placebo-controlled study. *J Intern Med* 1992;**231:**261–7.

20 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.

21 Haskell WL, Luskin FM, Marvasti FF. Complementary and alternative therapies for cardiovascular disease. In: Spencer JW, Jacobs JJ (eds). *Complementary/alternative medicine: An evidence based approach.* Philadelphia:Mosby Yearbooks; 1999:94.