EDTA Chelation Therapy in the Treatment of Vascular Disease

Ethylenediamine tetraacetic acid (EDTA) chelation therapy has been used for decades for the treatment of vascular disease, alone or in combination with other treatments. This article includes a historic review of the research literature, current evidence of effectiveness, potential mechanisms of action of EDTA, and some brief case reports. The authors conclude that EDTA chelation therapy is a valuable therapeutic option for vascular disease, either alone or in conjunction with standard treatment protocols. Key words: *angina, atherosclerosis, chelation, claudication, EDTA, vascular disease*

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CHELATION is defined as the incorporation of a metal ion into a heterocyclic ring structure. Living systems use chelates commonly, for example, in many enzyme functions and in the structure and function of heme (a chelate of iron) and chlorophyll (a chelate of magnesium). Ethylenediamine tetraacetic acid (EDTA) is a synthetic amino acid with chelating properties. It was first used clinically for the treatment of lead toxicity before 1950 and was reportedly used for control of hypercalcemia in 1950.[1]

It was noted that patients being treated with EDTA for lead toxicity reported improvement, apparently coincidentally, in angina pectoris. That observation began the investigation of the use of EDTA in the treatment of atherosclerotic vascular disease. As a result, the first study of the use of EDTA in atherosclerotic disease was published in 1956. Clarke et al[2] reported on the results of chelation therapy in 20 patients with confirmed disease, 19 of whom improved as measured by physical activity. They stated "A placebo action seemed improbable for several reasons. There was slight if any clinical improvement until after the discomfort of 20, and with a few, 30 infusions. A patient's progress was based on measured physical activity rather than appraisal of subjective symptoms. The improvement gained has been retained and expanded in all, and a few for as long as 2 years. The results have been uniformly good."[2(p665)]

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In 1960, Meltzer and colleagues[3] published a favorable report on the use of EDTA chelation therapy in atherosclerosis. Although their patients did not show benefit during the initial treatment, at the end of 3 months 9 of the 10 patients were significantly better than before treatment as measured by a decrease in the number and severity of anginal episodes, reduced nitroglycerin use, increased work capacities, and in 8 of the patients, improvement in the electrocardiogram (ECG). Specifically, the ST and T waves improved, with inverted T waves reverting to the upright position.

In 1963, Kitchell and associates[4] reappraised their study of 1960. They also added 28 new patients to their study group. They concluded that EDTA chelation was not more effective than standard treatment for cardiovascular disease. However, their data do not support their revised conclusions. Cranton and Frackelton[5] reviewed Kitchell and colleagues' reappraisal. "The majority of patients in the 'reappraisal' were reported to have improved and to have maintained improvement following therapy. After 18 months with no further therapy and with no stated dietary or risk factor modification, 46 percent of a group of 28 patients remained improved [ECG improvement in 46%, in addition to improvement by subjective report in 64% of subjects and increased exercise tolerance in 64%]."[(p 108)] These were high-risk patients, and they received only 20 treatments prior to evaluation. Cranton and Frackelton concluded that EDTA resulted in progressive improvement over time rather than the improvement and stabilization that is typically seen with standard treatments such as bypass surgery and balloon angioplasty.

Besides not initiating a process that results in progressive improvement, the usual treatments for vascular disease, whether coronary, cerebral, or peripheral, are expensive and have some associated morbidity and mortality. In addition, they are not uniformly effective. A review of the medical literature reveals the following data:

- Coronary artery bypass surgery has an average mortality of 4% to 10%,[6] with mortality highest among older patients.[7]
- Coronary bypasses commonly restenose within 7 years.[8] Some patients, particularly older people, experience significant cerebral dysfunction after the procedure.[9]
- Angioplasty is not typically indicated for multivessel disease, and restenosis rates remain as high as 30% within 6 months.[10]
- Coronary bypass surgery commonly costs between $30,000 and $50,000.[11]

In the past 20 years, cardiovascular mortality has declined.[12] Ornish and Brown[13] suggest that this decline may be more of a result of life-style changes (ie, exercise, decreased fat consumption, decreased smoking) than to new therapeutic interventions. The statistics suggest the need to explore other therapeutic options. The integration of EDTA chelation therapy as part of standard treatment may decrease the necessity for more invasive approaches and make treatment safer and more cost-effective than current options. EDTA could enhance clinical outcomes because it offers the unique advantage of progressive improvement.

A literature review by Cranton[14] demonstrates that EDTA and other chelating agents are effective in treating vascular disease and that the treatment is dramatically effective in certain patients. When given according to the published protocol,[14] EDTA is safe, with a mortality rate that approaches zero and minimal morbidity. In approving the recent investigatory new drug (IND)

application for EDTA, the U.S. Food and Drug Administration did not require any further safety studies. The cost of a series of 25 to 50 treatments is approximately $2,000 to $5,000. These data suggest that EDTA is a treatment worthy of further investigation. However, to date there are no large well-designed, randomized, double-blind controlled trials comparing EDTA chelation therapy with bypass surgery or balloon angioplasty in the treatment of vascular disease.

EVIDENCE OF EDTA EFFECTIVENESS

Chappell and Stahl[15] conducted a meta-analysis of 41 studies of EDTA chelation therapy in patients with vascular disease. Nineteen of the studies, with a total sample of 22,765 patients, met the criteria for inclusion. Overall, 87% of the patients had measurable improvement with treatment. The correlation coefficient was high positive at $r = 0.88$, demonstrating a significant relationship between EDTA chelation therapy and symptomatic improvement. Because excluding unpublished data might lead to publication bias, a follow-up study[16] on 1,241 patients from 32 investigators was conducted. That study showed a correlation coefficient of $r = 0.88$, and 88% of the patients improved as measured by a variety of parameters (ie, ECG, ankle/brachial index, walking distance, exercise activity, Doppler testing, and others). The conclusion from both studies was that EDTA is effective in treating vascular disease.

Several individual studies are particularly significant and deserve further discussion. Olszewer and Carter[17] published a large study of 2,870 patients who had various chronic degenerative diseases but primarily vascular disease. Almost 90% of the patients showed good to excellent improvement as measured by walking distance, ECG, and Doppler changes. Olszewer and colleagues also completed a small blinded, cross-over study[18] with peripheral vascular patients that demonstrated significant improvement in both walking distance and ankle/brachial index measurements. Another investigator documented improvement following EDTA using the double- and triple-product on treadmill testing.[19] Rudolph and associates[20] demonstrated a 30% average reduction in carotid artery stenosis as measured by Doppler ultrasound testing before and after EDTA treatment in 30 patients. Rudolph et al[21] published a case study with retinal photographs showing significant improvement in macular degeneration following EDTA therapy. Casdorph used technetium 99 isotope techniques to evaluate EDTA treatment in both coronary[22] and carotid[23] disease. Both studies demonstrated significant improvement in arterial flow. The patients with coronary artery stenosis experienced an improvement in ejection fraction.

A number of articles have appeared showing the benefits of iron chelators in vascular disease. Brittenham and associates[24] used deferoxamine to prevent vascular complications in patients with iron overload. Because iron is a free-radical initiator and EDTA is an iron chelator, this chemical reaction may partly explain the reported beneficial results from EDTA therapy.

Other investigators have shown no benefit from EDTA chelation. A Danish study, published first under Sloth-Nielson and associates[25] and in more detail by Guldager and associates,[26] and a New Zealand trial by van Rij and associates[27] were reported as randomized, well-controlled, double-blind clinical trials. Even though 50% to 60% of treated patients improved, these trials did not support the effectiveness of chelation treatment because of very high response rates in the placebo groups. Both studies

were primarily of smokers who had severe disease and who were given only 20 treatments. Although there may be improvement in some patients after 10 to 20 treatments, standard therapy by trained chelating physicians is usually 30 treatments and may be 40 or more treatments in patients with severe disease. Furthermore, the fact that many of the patients in these two trials were smokers greatly limits the usefulness of the studies because smokers are known to have a poorer response to EDTA treatment than nonsmokers. The Sloth-Nielsen/Guldager study did not follow the American College for Advancement in Medicine protocol for EDTA treatment, although the investigators claimed to do so. The study has been criticized in at least four journals[28–31] and also by the Danish Committee on Scientific Dishonesty.

van Rij's trial was claimed to be placebo-controlled but actually compared two chelating solutions, one with EDTA and the other with thiamin and ascorbate for the treatment of peripheral vascular disease. Both groups of patients showed significant overall improvement (EDTA 60% versus thiamin/ascorbate 59%). Had these results been compared with a true placebo, chelation may have been shown to be significantly better than placebo.

Importantly, the patients in the EDTA chelation group studied by van Rij improved significantly in five of the studied parameters including resting ankle/brachial indices in both better and worse legs, two different parameters of physical activity, and femoral pulsatility indices, compared with the control group. Furthermore, none of the patients in the EDTA group worsened except one patient in one parameter (ankle/brachial indices in worse leg), although this was not true for the control subjects. Recently acquired raw data from this study reveal that 26% of the EDTA group achieved greater than 100% improvement in walking distance, compared with only 12% of the controls. A decreased ankle/brachial index was seen in only 6% of the EDTA group compared with 35% of the control subjects. Among the nonsmokers or those who had stopped smoking, 66% of the EDTA group improved with an average of an 86% increase in distance walked, but only 45% of the control subjects improved with an average of 56% increase in distance walked. Although van Rij's conclusion was negative, his data support the therapeutic effect of chelating solutions in patients with vascular disease.

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Hancke and Flytlie[32] treated 65 patients with chelation therapy who were on the waiting list for bypass surgery for an average of 6 months. Eighty-nine percent (n = 58) of these patients were able to cancel their surgery because of symptomatic improvement. Similarly, they chelated 27 patients who were recommended for amputation, and 24 affected limbs were saved. Chappell[33] estimated that if similar results were obtained in the United States, 363,000 of 407,000 bypasses would have been avoided and 102,000 limbs would have been saved with the use of chelation therapy in such patients in 1992. The direct cost savings in that year alone could have been as much as $8 billion. The only plausible explanations for Hancke's data are that not all surgery is necessary or that the EDTA treatment is highly effective, or both.

A recently published report by Escobar et al[34] showed a marked improvement in ankle/brachial indices in 76 of 80 patients ($P = 0.001$) treated with chelation therapy. The pulse oscillographs of the posterior tibial and dorsalis pedis arteries also improved. Twenty-eight of the diabetic patients had inoperable tibial artery lesions, and of those, 10 already had undergone amputation. Three of the patients had Leriche's syndrome. It is noteworthy that no patients suffered significant side effects from EDTA therapy, and renal function was not impaired except for a temporary reduction in creatinine clearance of 30% to 50% in six patients, which returned to normal within 30 days. The authors concluded, "Because of the good results obtained, we consider that chelation with EDTA represents another alternative to treating arterial insufficiency due to atherosclerosis. This is especially effective in patients who are unable to be treated surgically, or also can be a complement of the surgical procedure."[34(p61)]

MECHANISMS OF ACTION

EDTA therapy has multiple mechanisms of action that may positively affect plaque formation and cell membrane function. Kaman and associates[35] demonstrated the removal of metastatic calcium from rabbit aortas. Kindness and Frackelton[36] measured a significant inhibition in platelet aggregation and an extended partial thromboplastin time. Gutteridge[37] showed increased effectiveness of hydroxyl-radical scavengers in the presence of EDTA. Rudolph and associates[38] documented a reduction in iron following EDTA chelation treatment. Reduced iron load is one of the potential mechanisms of the antioxidant effect of EDTA.

Free radicals have been shown to cause coronary endothelial injury after cardiopulmonary bypass and ischemic cardioplegia.[39] Grech and associates[40] have demonstrated a marked increase in free-radical activity after primary coronary angioplasty in acute myocardial infarction. Because chelating agents can often control free-radical activity, they would appear to be useful agents to improve outcomes in patients with coronary artery disease,[41–43] even those undergoing other therapies. Others have demonstrated improved lipids[44] and the restoration of electromagnetic potential across cell membranes.[45] Several detailed reviews of these mechanisms have been published.[46–49]

Well-designed, randomized studies of chelation therapy have been initiated,[16] with the cooperation of U.S. Food and Drug Administration. Other studies have been designed and are about to be implemented with funding from government sources and the American College for Advancement in Medicine (S. Olmstead, MD, personal communication, April 1995). Even without these studies, the above evidence is sufficient, with informed consent, for the off-label use of chelating agents in the treatment of vascular disease.

INDICATIONS, CONTRAINDICATIONS, AND SIDE EFFECTS

Aside from heavy metal exposure, the primary conditions that are helped by chelation therapy include cerebral, peripheral, or coronary vascular disease.[14] Patients with scleroderma, rheumatoid, and osteoarthritis may also benefit from treatment with EDTA. EDTA is safer than other chelating agents that have been used for rheumatoid disease. Sometimes healthy persons ask for chelation therapy for preventive medicine. Because chelation removes heavy metals to which most people have been exposed, it may be reasonable to treat such patients with EDTA.

Unless someone is allergic to EDTA, which is rare, the contraindications to chelation are relative. Renal impairment is the most critical factor in safe treatment, and doses of EDTA must be modified according to the level of impairment as measured by the creatinine clearance. Patients with creatinine clearance <30 mL/minute or a creatinine level >2.8 mg/dL should be treated only with low-dose EDTA and only by experienced specialists.

Severe liver disease with significant elevation of liver enzymes and bilirubin is another contraindication to EDTA chelation treatment. In animal studies, EDTA has been shown to be teratogenic in the absence of adequate zinc. Thus, in pregnancy EDTA is contraindicated except in the treatment of severe lead toxicity.

Congestive heart failure patients need to be monitored carefully during any chelation treatment because of the fluid and sodium load inherent in the intravenous use of EDTA. Appropriate use of diuretics and monitoring of fluid and electrolytes is essential in such patients. With reasonable care and appropriate carrier solutions, such patients can usually be treated safely.

Potential side effects of chelation with EDTA are hypocalcemic tetany from too rapid infusion, nephrotoxicity, local thrombophlebitis, hypotension, and hypoglycemia. Most of these side effects are readily avoided or easily managed. Hypocalcemia is easily reversed with calcium infusions. Hypotension is usually mild, and slowing the infusion usually is adequate to prevent any significant problem. Patients are advised to eat before treatment and to bring snacks to eat during the 3-hour infusion. These measures are usually sufficient to prevent any serious fall in blood glucose.

All patients receiving EDTA need to be replenished with those minerals that are either removed by chelation treatment or imbalanced by other supplements, such as zinc, manganese, copper, chromium, and selenium. Iron supplements should be avoided unless there is a demonstrated iron deficiency. It is usual to supplement with synergistic antioxidants and B-complex vitamins at the same time.

DRAMATIC CASES

Most physicians who offer chelation therapy have treated at least several patients who have had multiple cardiovascular surgical procedures and been told that there was nothing else to be done. The only option offered was for them to go home to die. Even with these patients, however, chelation is often successful. One of the authors (LTC) has treated two patients with EDTA while they were awaiting heart transplants. Both improved significantly after treatment, were removed from the transplant waiting list by their cardiologists, and now lead active and productive lives. Another patient, a 59-year-old man, had been a hospital inpatient for 360 days of the 3-years preceding EDTA treatment. He had a past history of five myocardial infarctions, seven angioplasty procedures, and one bypass surgery. In the 2 years after EDTA treatment was begun, he was in the hospital for only 2 days (for noncardiac pain). As of this writing, he takes no medication and is able to bowl and play golf for the first time in years. Interestingly, his insurance company paid all of the $600,000 bill for 3 years of hospital care and refused to pay any of the $5,000 he spent on the successful EDTA treatment.

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EDTA chelation therapy is a safe and valuable addition to treatment protocols for all types and severity of vascular dis-

ease. However, it is neither miraculous nor infallible, and it must to be administered appropriately for safety and effectiveness. Physicians who use it must be well-trained.[14] The American Board of Chelation Therapy has a rigorous certification process to identify specialists in the field. As with any treatment for heart and blood vessel disease, it is part of a comprehensive program that includes lifestyle changes and beneficial medications. Overall, 87% of patients who use the treatment demonstrate improvement with objective testing. Many are able to reduce medications and significantly improve function. Others are able to avoid surgery or improve greatly even though they have previously responded poorly to standard treatment.

EDTA chelation therapy does not preclude the use of surgery, and in spite of receiving chelation treatments, some patients will require surgical interventions. There is usually time for patients to try chelation therapy before surgery or amputation, as Graboys and associates found in 1987 and 1992.[11,12] The authors of this article believe that adequate data exist to support this recommendation. In addition, patients who are not surgical candidates and who are doing poorly often benefit from chelation therapy. A trained physician uses EDTA in a comprehensive program that includes lifestyle modification and rational pharmacotherapy. This approach offers great potential benefit and is quite safe. It is also relatively inexpensive and does not interfere with other treatments.

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