OLWIN

THE WHITE HOUSE
WASHINGTON

JENNIFER

PLEASE ACKNOWLEDGE receipt directly.

Thanks,
J.

May 24, 1995

Dr. John H. Olwin
9631 Gross Point Road
Skokie, Illinois 60076

Dear Dr. Olwin:

Thank you for writing and sharing your suggestions regarding a way to "bypass" health care costs accrued due to heart disease. This Administration remains determined to fulfill the fundamental principle of reform -- guaranteed private health care coverage for all Americans.

To give your ideas the proper attention, I have taken the liberty of forwarding your letter to the appropriate health policy staff at the Office of Domestic Policy. I can assure you that your thoughts will receive careful consideration.

Thank you again for taking the time to write. I will keep your views in mind.

Sincerely,

Leon E. Panetta
Chief of Staff

cc: Office of Domestic Policy

LEP/tab

John H. Olwin, M.D.
9631 Gross Point Road
Skokie, Illinois 60076
1-708-676-4030

MAR 13 1995

March 7, 1995

Mr. Leon Panetta
Chief of Staff
The White House
Washington D.C.
20500

Dear Mr. Panetta:

I very much enjoyed your interview Sunday on the David Brinckley program and thought you handled the questions from Sam Donaldson particularly well.

You have probably one of the most difficult positions in the Administration and are probably better qualified for the job than anyone who has tried it in this century. Quite a statement, but many of my friends would agree.

Certainly, one of your most difficult problems at present is that of Health Care. There is no easy solution to it, but having been a part of it for sixty years I have a few suggestions about one of the most pressing and costly problems in the field today,.. that of coronary artery "bypass'. As you well know, most of these operations are done on patients over 60 years of age and each costs $65,000 or more. Some individuals have gone through the procedure two, three and more times, at the above or greater cost.

There is a procedure that will almost surely prevent or materially reduce the development of atherosclerotic obstruction of the coronary arteries in most if not all individuals. It has been neglected and or scorned by most of the medical profession, largely because it has not been given an acceptable trial. The accompanying material may answer questions as to its possible efficacy and cost.

I would suggest that two committees composed of competent physicians be chosen. One committee would organize a controlled

clinical study of patients who are candidates for coronary by-pass. Half of those candidates would proceed with the by-pass. The other half will be given infusions of EDTA (ethylene diamine tetra acetic acid). The second committee would judge the results of the two procedures. Within one year following the completion of the two procedures the comparative benefits of them should be apparent.

I have no doubt as to the outcome of the trial. And I believe that the resulting changes in our methods of treatment of patients with *any* type of atherosclerosis will result in at least an eighty-five (85) per cent reduction in the present cost of such treatment.

Thank you for giving your time and attention to this letter. So that your advisors in the fields of Health Care may have some basis for judging my competence to write on such matters I am taking the liberty of enclosing my Resumé.

Most respectfully,

John H. Olwin

John H. Olwin M.D.

RÉSUMÉ

John H. Olwin

Fields of competence: Trace metals; blood coagulation; general and vascular surgery, thrombo-embolism; atherosclerosis

Professional Experiences:

Private practice of sclerotherapy for varicosities and venous blemishes 1978 to present.
Private practice of General and Vascular surgery 1939 to 1984. Founder and Director of Clinical Coagulation Laboratory and of Coagulation Research Laboratory, Presbyterian, and then Presbyterian-St. Luke's Hospital, Chicago, Illinois,1946 and 1947 respectively to 1969. Attending Surgeon, Presbyterian-St. Luke's Hospital,1942 to 1972. Emeritus, General Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 1972 to present. Clinical Professor of Surgery, Rush Medical College,1942 to present. Consultant in General and Vascular Surgery, Veterans Administration Hospital, Hines Illinois, 1946 to 1962. Special interest in the role of essential and toxic metals and organics in cellular metabolism.

Education: B.A.University of Illinois,1929. M.D.University of Chicago (Rush Medical College) 1934. Internship, Presbyterian Hospital, Chicago, Illinois 1935 to 1936. Residency (General Surgery) 1937 to 1939. Research Fellow, Rush Medical College 1939-1940. Associate,General Surgery, Cook County Hospital, 1939 and 1940.

Professional Activities American Medical Association, Chicago Surgical Society, American College of Surgeons, Society for Vascular Surgery (Recorder 1960 to 1966), Central Surgical Society, Western Surgical Association, Chicago Medical Society, Illinois State Medical Society, Institute of Medicine of Chicago (Secretary, 1970 to 1972; President,1973 to 1975), Committee on Thrombosis and Hemorrhage, National Research Council, 1959 to 1964.

Military Service: Extended Active Duty M.C.AUS 1940 to 1946, .Lt.Col. Chief of Surgery, 29th Evacuation Hospital, Bronze Star, three Battle Stars.

Publications: Author or co-author of 151 papers in the areas of General and Vascular Surgery, Blood Coagulation, Trace Metals and Chronobiology.

CHELATION THERAPY

What is chelation therapy? It is the infusion of substances that remove metals from the body. The word is derived from the Greek word *chela*, the pincer claw of the crustean. Early investigaters saw a similarity between the way these chemical agents bind metals and the way the crustacean firmly fixes its prey. The metals are so firmly bound that it is difficult for other chemicals to break that bond. Chelating agents have been used in industry for many years to separate metals from ores or from other metals.

The exact nature of the chemical action on the body, other than the binding of metals, is not well understood. There are several theories. The one I hold to is that we are removing toxic metals which have replaced, in the various enzyme systems, the essential metal(s) necessary to the normal functioning of that particular enzyme system.. There are, at the present time, 15 trace metals that are known to be essential to normal enzyme activity. Among these are cobalt, chromium, iron, molybdenum, manganese, nickel, selenium, tin and vanadium. Every cell contains more than 3000 enzymes and of these more than fifty per cent are so-called metallo-enzymes. In these enzymes the metals are structural components of the enzyme system. The remaining enzymes are probably influenced by metals acting as co-enzymes or as catalysts. Thus, almost no process goes on in the body without the aid of metals. If these essential metals are replaced by toxic ones such as lead, cadmium, mercury, aluminum or even an overwhelming amount of some of the other metals, even the essential ones, these enzymes are paralyzed. If we can remove these metals that are acting as poisons, perhaps we can restore the enzyme systems to their normal or near-normal activity and thus reverse the disease processes. In removing the toxic metals, we also remove a number of the essential ones. These, however, can be replaced by the food that we eat and by the addition to our dietary routine of so-called nutrient supplements, i.e. vitamins and minerals.

It would be a happy circumstance if we could feed this chelating agent by mouth. However, when given orally most of it passes through the intestinal tract without being absorbed and, in passing, binds a number of the essential elements that we need. Hence, it becomes necessary to give it either intramuscularly or intravenously. Since the intramuscular route is painful and is less well controlled, we give it intravenously. This is an inconvenience and an expense but it is also painless and, being more easily controlled, is much safer than the intramuscular route. The inconvenience is that the patient must sit with a needle in his/her

vein for a period of three hours for an infusion. Since the material that we use is an acid, even though a weak one --ethylene-diamine-tetra-acetic acid (EDTA)-- it must be given slowly so as not to be painful and so as to allow the body to absorb it more completely rather than excreting it too rapidly. Unlike most drugs, it is not broken down in the body into its component parts, but is excreted just as it is given except that it has firmly bound a number of metals. It is excreted in the urine and can be recovered (almost 100 per cent of it) in a relatively short period of time (hours). When properly given it is entirely safe. Its only toxic effect is on the kidneys and since we give it slowly and monitor each patient's kidney function with each infusion, the hazard is reduced to zero. In fact, we have some patients with badly damaged kidneys who, when given the material cautiously, have been able to accept it and have experienced an improvement in their kidney function.

it has been observed by competent investigators that arteries in human beings obstructed by calcium and lipid (fat) deposits will, over a period of months to years, become patent and will for the most part remain so as long as the EDTA infusions are continued. The artery walls will again be narrowed and the obstruction will recure by similar calcium and lipid deposits if the infusions are discontinued. These findings have been repeated in rabbits fed an atherogenic diet. As stated earlier, one of the principle effects of the infusion of EDTA is the removal of toxic metals such as lead, cadmium, aluminum and mercury from the body, thus restoring normal enzyme function. There is no doubt that all persons and animals living in the cities of western civilization have elevated levels of such metals. Some years ago we did a study of 100 patients in Chicago and suburbs and found an elevated level of lead (the "normal" then being 0 to 80 micrograms per 24 hour specimen of urine} in 87 per cent of them. Sheep grazing near a freeway have been found to have a heavy body-burden of lead. EDTA has been used by the medical profession for years as the best treatment available for lead poisoning. Another study from our laboratory showed that cholesterol and all other blood lipids were significantly lowered following the beginning of chelation therapy and remained lowered as long as the therapy was continued. The lipid levels returned to their former state about three weeks after the infusions were discontinued. Other benefits following the initiation of chelation therapy that I have observed have included the unblocking of atherogenic obstruction in main leg arteries; dissolution, overnight, of freshly lodged emboli; increase in collateral circulation, color and warmth to a limb, and termination of gangrene; observed status-quo of an abdominal aortic aneurysm in a patient on regular chelation therapy over a period of thirty years; improvement in or elimination of claudication; improvement in sexual desire and performance in men and, in a very limited number of adults,

improvement in, or elimination of, the symptoms of Alzheimer's Disease.

Unfortunately, the EDTA infusions must be continued in order to maintain their various benefits. Nobody knows how often treatment must be given. Over the years I have found that, after the initial series of 20, one infusion every two weeks has been adequate. A few patients have seemed to do well on monthly infusions. All of those who have stopped the treatment completely have, within two to three years, developed arterial closures and a return of their previous conditions.

It is interesting to speculate on the possible influence of universal chelation therapy on the health of the nation and on the national health bill. At the current cost, the latter would be in the neighborhood of $2500 to $3000 per person,per year, much less with universal utilization. A coronary artery by-pass operation currently costs $60,000. Other possible benefits of the elimination of toxic metals in the body and the improvement of enzyme function are mind-boggling. Fortunately infusions are easily and simply administered and can be set up in every hamlet in the country.

As with Edward Jenner's claim in his discovery of smallpox vaccination in the late 1770's and that of Louis Pasteur a century later, when he told the doctors and mid-wives they were carrying child-bed fever from patient to patient because they did not wash their hands between cases, ...original scorn and disbelief, by the medical profession, will eventually turn to the acceptance of EDTA-chelation therapy as a valuable and useful tool in the treatment of a number of clinical abnormalities.

John H. Olwin M.D.
Clinical Professor of Surgery
Rush Medical College

For those who may wish to look further into the scientific bases for, and the benefits of chelation therapy it is recommended that he/she order a copy of a collection of papers by various scientists in the field. It is 'A Textbook on Chelation Therapy" edited by Elmer M. Cranton with a foreword by Linus Pauling. It can be obtained from the American College of Advancement in Medicine, Edward A. Shaw,M.B.A., Ph.D. Executive Director, 23121 Verdugo Drive. Suite 204, Laguna Hills, Ca. 92653 714 583 7666. The cost is approximately $25.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

CHELATION THERAPY - AN INFORMAL SUMMARY

The goal of chelation therapy for treating arteriosclerosis (or atherosclerosis) is decreasing the narrowing of arteries by the removal of calcium. Calcium is present in some arteriosclerotic lesions. The drug used, disodium EDTA (disodium edetate, Endrate) grasps or binds calcium, and the hope is that it will grasp calcium from these areas of arterial obstruction.

Such "chelation therapy" is commonly accompanied by other therapies, such as trace element "supplements," large doses of vitamins and dietary modifications. Nevertheless, the central element of "chelation therapy" is repeated intravenous infusions of disodium EDTA.

There is no sound evidence that chelation therapy works -- that it is effective or has clinical benefit.

There is also an important fallacy in this underlying idea. When disodium EDTA is administered intravenously, it encounters calcium everywhere in the blood and it binds calcium from the blood, not from the tiny deposits of calcium that may exist in arteriosclerotic lesions. The bound calcium is removed from the body through the kidneys. The calcium in blood is replenished by calcium from the bone, which is easily accessible to the blood stream, or by calcium from the gut.

The advocates of "chelation therapy" have testimonials from people who feel that their symptoms have been relieved. However, there is no clinical trial or clinical study with scientific merit that has shown the purported beneficial effects. Until August, 1991, the best study was published in 1963. It concluded that "we believe that chelation as used in this study did not benefit patients more than other commonly used therapeutic methods. It is not a useful clinical tool in the treatment of coronary artery disease at the present time". By today's standards, that study has some shortcomings but there is no subsequent study to contradict those results. In August, 1991 and early 1992, reports were published of a large, scientifically sound clinical trial that carefully documents that chelation therapy does not work. Symptoms, clinical findings, x-rays, and other measurements were compared in patients who received the chelation therapy and compared to similar measurements in patients who received a "dummy" therapy instead of chelation. The results were identical; chelation therapy was shown to be of no value.

What about people who have felt better following chelation therapy? In the objective assessment of a variety of medical therapies, including some for arteriosclerotic disease, people have often felt much better in response to sham therapy or "placebos." Indeed, the more dramatic the intervention, the more likely the effect. The more someone has invested in feeling better -- and a course of chelation therapy may be on the order of 30 to 50 intravenous infusions over several months and costs thousands of dollars -- the more likely a person is to be convinced that there has been a benefit.

It might be noted that "chelation" is a chemical term meaning that a compound grasps a metallic element to form a ringed structure. In that sense, some forms of chelation are accepted and appropriate forms of therapy. For example, deferoxamine is a validated therapy in the management of iron overload following repeated blood transfusion and EDTA, similar to that used in chelation therapy of arteriosclerosis, is appropriate and accepted for the treatment of lead poisoning.

This has nothing to do with the alleged benefits of chelation in the management of arteriosclerosis. There is no reason to expect benefit from chelation in the management of arteriosclerosis. More importantly, there has been no scientific evidence of such benefit -- and now there is scientific evidence of no benefit.

June 1992

FROM: Peter L. Frommer, M.D.
Deputy Director, NHLBI

Secretary - Theresa Raymer

Bldg. 31, Rm. 5A49
Phone (301) 496-1078
Fax (301) 402-3686

TO: M.S. Zoe Neuberger

FAX: 202-456-7431

DATE: 6-26-95

This transmission has 5 page(s) (including this cover sheet).

NOTE:

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

BLDG 31, ROOM 5A49

PHONE 301-496-1078
FAX 301-402-3686

June 26, 1995

Ms. Zoe Neuberger
Domestic Policy Council
Room 212A
Old Executive Bldg.
Washington, D.C. 20500

Dear Ms. Neuberger:

As promised over the telephone, I am enclosing a letter as I would respond to the query on chelation therapy that you had forwarded to Dr. Sopko.

A hard copy of the enclosure is being sent so that you may send that if that's your choice.

I am also including copies of the articles referenced, as well as a couple of other articles that may give you a bit of insight -- a one-page summary published in the ACP Journal Club (which is sent to all members of the American College of Physicians) that summarizes the reports out of Denmark; a review by Grier and Meyers (which is a nice review, but its last paragraph -- or at least its last two sentences -- could have been omitted); a one-page summary in The Medical Letter; and a little piece by Patterson (Can. Med. J. 1989). I am not sure whether it is worth sending these further to Dr. Olwin, but I thought you might be interested.

Sincerely,

Peter L. Frommer

Peter L. Frommer, M.D.
Deputy Director

Enclosures

D R A F T

BLDG 31, ROOM 5A49
PHONE 301-496-1078
FAX 301-402-3686

June 26, 1995

John H. Olwin, M.D.
9631 Gross Point Road
Skokie, Illinois 60076

Dear Dr. Olwin:

I am responding to your recent letter to Mr. Panetta.

At the National Heart, Lung, and Blood Institute, we have followed the scientific literature on chelation for the treatment of heart and vascular disease for more than 25 years. There are proponents of chelation therapy who have made very strong claims for its effectiveness. However, the only scientifically sound research on chelation therapy for the treatment of atherosclerosis has demonstrated no beneficial effects when compared to similar patients who received a dummy or placebo therapy instead of chelation.

I am enclosing a copy of our informational summary on this topic. Since the date of that report, another scientifically sound study has been published, comparing results in patients with atherosclerosis involving arteries of the lower extremities who received either active drug or placebo. Again, in a scientifically sound study in which patients were treated with active drug or placebo, no differences were found in outcomes.

The vast majority of research sponsored by the NIH is investigator-proposed, i.e., the investigator proposes the research and, if his or her application is successful in competing for funding, carries out the research. Individuals interested in conducting research on chelation therapy may submit a research grant application to the NIH. I can recollect only two such applications among more than forty thousand that we have received since we have been following this topic. That hardly closes the door on future research, but frankly, it is hard to be very optimistic about the prospects for effectiveness of chelation in the management of atherosclerosis.

Sincerely,

Peter L. Frommer, M.D.
Deputy Director

P.S. Above I am referring to the reports from Denmark (Guldager, et al, J. Intern. Med. 231, 261-267, 1992 and Sloth-Nielsen, et al, Am. J. Surg. 162, 122-125, 1991) and from New Zealand (van Rij, et al, Circulation 90, 1194-1199, 1994).

Enclosure

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Peter L. Frommer, M.D.
Deputy Director

Enclosures

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Deputy Director

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Enclosure

Journal of Internal Medicine 1992; 231: 261–267

EDTA treatment of intermittent claudication – a double-blind, placebo-controlled study

B. GULDAGER, R. JELNES*, S. J. JØRGENSEN, J. S. NIELSEN†, A. KLÆRKE*, K. MOGENSEN‡, K. E. LARSEN§, E. REIMER¶, J. HOLM** & S. OTTESEN

*From the Department of Surgery, Central Hospital Hillerød, Hillerød, the *Department of Vascular Surgery V, Aalborg Hospital Syd, Aalborg, the †Department of Surgery, Skejby University Hospital, Aarhus, the ‡Department of Surgery L, Bispebjerg Hospital, Copenhagen, the §Department of Surgery, Kolding Hospital, Kolding, the ¶Department of Surgery, Slagelse Hospital, Slagelse, and the **Department of Surgery, Gentofte University Hospital, Copenhagen, Denmark*

Abstract. Guldager B, Jelnes R, Jørgensen SJ, Nielsen JS, Klærke A, Mogensen K, Larsen KE, Reimer E, Holm J, Ottesen S (Department of Surgery, Central Hospital Hillerød, Hillerød, Department of Vascular Surgery V, Aalborg Hospital Syd, Aalborg, Department of Surgery, Skejby University Hospital, Aarhus, Department of Surgery L, Bispebjerg Hospital, Copenhagen, Department of Surgery, Kolding Hospital, Kolding, Department of Surgery, Slagelse Hospital, Slagelse, and Department of Surgery, Gentofte University Hospital, Copenhagen, Denmark). EDTA treatment of intermittent claudication — a double-blind, placebo-controlled study. *Journal of Internal Medicine* 1992; **231**: 261–267.

A double-blind, randomized multicentre study was undertaken to evaluate the possible effect of chelation treatment with ethylenediamine-tetraacetic acid (EDTA) in patients with severe intermittent claudication. A total of 153 patients received 20 intravenous infusions of either 3 g Na_2EDTA or placebo during a period of 5–9 weeks. Vitamin, mineral and trace element supplements were administered orally. The changes observed in the pain-free and maximal walking distances, measured on a treadmill, were similar in the two groups. During the 3-month ($n = 149$) and 6-month ($n = 123$) follow-up period, no long-term therapeutic effect of EDTA could be demonstrated. The ankle-brachial blood pressure index remained unchanged throughout the study period. This study failed to demonstrate any effect of EDTA chelation treatment in intermittent claudication.

Keywords: atherosclerosis, chelation therapy, ethylenediamine-tetraaceticacid, intermittent claudication.

Introduction

Ethylenediamine-tetraaceticacid (EDTA) is an amino-acid complex with high affinity for divalent cations (e.g. Pb^{2+}, Ca^{2+}, Mg^{2+}), with which it forms complexes that are eliminated in an unmetabolized form by the kidney ($T_{\frac{1}{2}} = 1$ h) [1–5]. EDTA is poorly absorbed from the gastro-intestinal tract, and should therefore be administered intravenously [3]. EDTA is well established in the treatment of lead intoxication [6], but may cause hypocalcaemia [5], and has nephrotoxic side-effects [5–10].

Since the 1950s, many case reports have suggested that EDTA can relieve symptoms caused by atherosclerosis [11–19]. To our knowledge, no controlled clinical trial on the possible effect of chelation therapy in atherosclerosis has been published [8–10]. However, in the USA and other countries, including Denmark, several private clinics offer EDTA chelation therapy for atherosclerosis, at significant financial cost to the patient. Due to the considerable interest in this field, we considered it necessary to conduct a randomized, double-blind, placebo-controlled study of chelation therapy in peripheral vascular disease (PVD).

Study population

All patients included in the study were more than 40 years of age, and had suffered from stable intermittent claudication (IC) for at least 12 months.

The pain-free walking distance (PWD) was in the range 50–200 m, measured on a treadmill at a speed of 3.6 km h^{-1} (1 m s^{-1}), with an inclination of 10°. The maximal walking distance (MWD) was measured at the same time. The ankle/brachial blood pressure index (A/I) of the worse leg was less than 0.8, measured by either the strain-gauge or Doppler technique.

During the 10-month period from June 1989 to April 1990, 159 patients (56 women and 103 men) from seven departments of vascular surgery in Denmark fulfilled these criteria and entered the study (Hillerød, 55 patients; Skejby, 30 patients; Aalborg, 25 patients; Bispebjerg, 19 patients; Kolding, 10 patients; Slagelse, 10 patients; Gentofte, 10 patients).

Patients receiving digoxin, prolonged acting nitrates, calcium antagonists or antihypertensives were only included if they had been on stable dosage for at least 4 weeks prior to the study. The exclusion criteria are listed in Table 1. The demographic data for the study population are listed in Table 2. No statistically significant difference could be demonstrated between the two groups.

The patients all gave their informed consent to participate in the study. The protocol was approved by the regional ethical committees.

Table 1. Exclusion criteria

Vascular surgery within the last 12 months
Ischaemic rest pain or gangrene
Moderate or severe venous insufficiency
Renal insufficiency
Diabetes mellitus
Thyroid and parathyroid disorders
Hepatic dysfunction
Significant cardio-pulmonary failure, e.g. acute myocardial infarction within the last year
Coexistent carcinomas
Tuberculosis within the last year
Pregnancy
Other conditions that could limit the patient's walking distance or reliable interpretation of the study
Patients receiving anticoagulants, nitroglycerine or lithium
EDTA chelation therapy within the last 24 months

Table 2. Demographic data on entry to the study

Parameter	EDTA	Placebo
No. of patients	80	79
Age (years)	64 ± 7	66 ± 9
Weight (kg)	70 ± 12	73 ± 12
Height (cm)	170 ± 10	171 ± 8
Sex		
Male	48	55
Female	32	24
Duration of IC (years)	4.8 ± 3.7	4.9 ± 3.6
Smokers (%)	68.8	69.6
Previous vascular surgery (no. of patients)	12	12

Data are expressed as mean values ± SD.

Study design

The design of the study was randomized, double-blind and placebo-controlled. The active treatment (verum) consisted of 3 g Na_2EDTA and 8.4 g NaCl in sterile water diluted to 1000 ml (isotonic solution); the placebo was 1000 ml isotonic saline. All solutions were prepared at the hospital pharmacy, Aalborg. The patients were randomized in blocks of ten. In order to prevent an EDTA-induced depletion of vitamins, trace elements and mineral supplements, the patients were given Multitabs® with magnesium (Ferrosan), one tablet daily, during the treatment period. The ingredients are listed in Table 3.

Before treatment, a physical examination was performed, together with the following serum and urine analyses: haemoglobin, thrombocytes, haematocrit, APTT (activated partial thromboplastin time), prothrombin (Factors II, VII and X), fasting glucose, fibrinogen, creatinine, albumine, calcium, phosphate, alkaline phosphatase, lactic dehydrogenase (LDH), and urinary stick-test for protein, blood and glucose.

Patients received verbal and written instructions regarding the importance of smoking cessation, physical training, dietary advice and weight loss, when applicable. The treatment took place in the out-patient department. The duration of a single treatment was 3–4 h, and a total of 20 infusions was given over a period of 5–9 weeks.

The treadmill and selected laboratory tests were repeated after the 10th infusion.

After the 20th infusion, the subjective effect of the treatment was evaluated by the patients using a rating scale from 1 to 5. Laboratory tests were repeated. After the treatment period and at 3 and 6 months, the following parameters were redeter-

Table 3. Vitamin, mineral and trace element content of each tablet (Multitabs ® with magnesium, as stated by the manufacturer, Ferrosan)

Vitamin A	1000 mcg
Vitamin B_1	1.5 mg
Vitamin B_2	1.7 mg
Vitamin B_6	2.2 mg
Vitamin B_{12}	3 mcg
Folic acid	100 mcg
Nicotinamide	19 mg
Pantothenic acid	6 mg
Vitamin C	60 mg
Vitamin D	5 mcg
Vitamin E	10 mg
Magnesium	100 mg
Iron	18 mg
Zinc	15 mg
Copper	2.5 mg
Iodine	150 mcg
Manganese	3.8 mg
Chromium	125 mcg
Selenium	125 mcg
Molybdenum	250 mcg

mined: PWD, MWD, A/I (calculated from the same leg as at entry), weight, medication, tobacco consumption, changes in diet and physical activity.

Statistical methods

The percental change in walking distances from pre-treatment to post-treatment, and the change in A/I post-treatment minus pre-treatment in each patient were evaluated by analysis of variance, taking into account sex, treatment and smoking status (present smoker or former smoker). To obtain a better fit to the Gaussian distribution, the percentage change in walking distance was log transformed.

Observations from patients who stopped walking for a reason other than pain presented a special problem, and were regarded as censored observations, i.e. PWD and MWD was at least the value observed. As the number of patients with censored observations was small, these data were excluded from the analysis. The age of the patient was entered into the variance model as a covariate; interaction terms between treatment and sex, and treatment and smoking status were also included. This complex model was gradually simplified by eliminating non-significant ($P \geqslant 0.05$) model terms. The changes in walking distance and A/I from pre-treatment to the 3-month follow-up and from pre-treatment to the 6-month follow-up were analysed in the same way, as were the separate ankle pressure and brachial pressure data. Differences between treatment groups were defined as EDTA minus placebo.

The subjective judgement of the therapeutic result in the two groups was compared by the Wilcoxon test.

Results

A total of 159 patients were recruited to the study, of whom 153 subjects completed the treatment period (EDTA, 75 patients; placebo, 78 patients). Six patients dropped out during the study period: five in the EDTA group (stroke, impaired renal function, mental disorder, dyspepsia and carcinoma of the prostate), and one from the placebo group (dyspepsia). During the 3-month follow-up ($n = 149$),

Table 4. Pain-free walking distance (m)

	EDTA (mean value ± SD)	Placebo	Ratio (95% confidence interval)
Pre-treatment (75/78)	74 ± 25	82 ± 36	
10th infusion (70/73)	97 ± 41	101 ± 53	1.04 (0.91–1.19)
Post-treatment (68/67)	93 ± 40	109 ± 56	0.91 (0.79–1.04)
3 months post-treatment (66/67)	95 ± 48	102 ± 42	0.98 (0.85–1.13)
6 months post-treatment (51/56)	97 ± 47	119 ± 93	1.04 (0.91–1.19)

Table 5. Maximal walking distance (m)

	EDTA (mean value ± SD)	Placebo (mean value ± SD)	Ratio (95% confidence interval)
Pre-treatment (75/78)	119 ± 38	157 ± 266	
10th infusion (70/73)	164 ± 79	192 ± 222	1.02 (0.90–1.15)
Post-treatment (68/67)	159 ± 99	206 ± 239	0.92 (0.81–1.05)
3 months post-treatment (66/67)	162 ± 101	204 ± 248	0.94 (0.82–1.08)
6 months post-treatment (51/56)	180 ± 150	194 ± 127	0.96 (0.79–1.16)

four patients dropped out (one death, two deteriorations leading to vascular surgery, and one patient who started EDTA chelation therapy at a private clinic).

The treatment code was broken when the last patient had completed the treatment period, but was not disclosed to the patients until the 3-month follow-up. Of the 123 patients who completed the 6-month follow-up, 36% were still blinded at that time.

Five patients in the EDTA group and three in the placebo group exhibited progression of PVD leading to vascular surgery 3–6 months after treatment. The remaining 16 patients did not turn up for re-examination as they considered their condition to have remained unchanged, confirmed by telephone interview.

The duration of treatment was 46 ± 8 days (range 31–69 days) in the EDTA group and 46 ± 8 days (range 27–63 days) in the placebo group. No significant changes were observed between the groups with regard to weight, medication, dietary intake, tobacco consumption or degree of physical activity during the study period.

Walking distances

The mean values for walking distances are presented in Tables 4 and 5. A non-significant increase in walking distance was observed in both the EDTA group and the placebo group from pre-treatment to the 10th infusion. Thereafter no changes took place.

In the last column of Tables 4 and 5 the difference between treatment groups with regard to walking distance (percentage change) is given. This difference is defined as the ratio percentage change in the EDTA group divided by the percentage change in the placebo group, compared to pre-treatment. This ratio has no dimension.

Post-treatment it was found that improvement in the placebo group was 1.1-fold (1/0.91) better than that in the EDTA group with regard to PWD, and the same (1/0.92) concerning MWD.

Ankle/brachial index (A/I)

The data for the changes in A/I are presented in Table 6. No significant changes took place during the study period, indicating that there were no changes in the macrovascular system.

Systemic and ankle blood pressures

The change from pre-treatment to post-treatment showed a significant effect of treatment group. The difference was estimated to be −8.82 mmHg (S.E.M. 3.15, $P = 0.006$). The raw average of treatment groups was −4.85 for the EDTA group and 3.41 for the placebo group.

At the 3-month follow-up the difference was estimated to be −1.18 (S.E.M. 3.87, $P = 0.76$) and at the 6-month follow-up the difference was estimated to be −1.37 (S.E.M. 4.37, $P1 = 0.75$). This means that the brachial pressure in the EDTA group was reduced by 8.82 mmHg more than that in the placebo group post-treatment.

The ankle pressure data showed a rather different pattern. The difference in change from pre- to post-treatment was estimated to be −4.99 (S.E.M. 2.33, $P = 0.03$). At the 3-month follow-up the difference was estimated to be −1.70 (S.E.M. 3.09, $P = 0.58$),

Table 6. Ankle-brachial index

	Pre-treatment	Post-treatment	3 months post-treatment	6 months post-treatment
EDTA	0.50±0.15	0.52±0.14	0.54±0.14	0.56±0.13
n	75	75	73	57
Placebo	0.51±0.13	0.52±0.14	0.53±0.14	0.53±0.14
n	78	78	76	66

Data are expressed as mean values ± SD.

and at the 6-month follow-up the difference was estimated to 0.04 (S.E.M. 2.85). This means that the ankle pressure in the EDTA group was reduced by 4.99 mmHg more than that in the placebo group post-treatment.

Subjective evaluation

Subjective evaluation of the treatment result did not differ between the groups ($P = 0.8$). In both groups, half of the patients considered that their IC remained unchanged, and the other half reported improvement of varying degree (Table 7).

Laboratory tests

Laboratory tests on entry to the study were in the normal range, and only alkaline phosphatase activity changed significantly during the study period. Alkaline phosphatase in the EDTA-treated group decreased from a mean value ± SD of 175 ± 55 U l^{-1} to 148 ± 42 U l^{-1} ($P < 0.001$). Due to symptoms of hypocalcaemia, eight patients received intravenous calcium gluconate (EDTA, 5 patients; placebo, 3 patients). One patient (EDTA group) showed subnormal calcium levels. In 3 patients (EDTA, 1 patient; placebo, 2 patients) creatinine levels increased after the 10th infusion, but normalized 8 d after cessation of treatment. In 11 patients (EDTA, 4 patients; placebo, 7 patients), creatinine levels increased after the 20th infusion.

Side-effects

Side-effects were observed (Table 8), but were generally non-specific and showed no preponderance in any of the groups. In particular, the incidence of phlebitis and pain at the infusion site, as well as gastrointestinal side-effects, were similar in the two groups. One patient developed Raynaud's phenomenon of two fingers after the third EDTA treatment; the symptoms persisted for 4 d and then gradually disappeared spontaneously. Another EDTA patient developed localized dermatitis on the nasal cheek fold after the sixth infusion; this disappeared spontaneously after the treatment period.

Table 7. Subjective evaluation

	EDTA	Placebo
Aggravation	1	0
Unchanged	38	39
Improvement		
Mild	19	23
Moderate	13	9
Great	4	7

Table 8. Side-effects during the treatment period

Side-effect	EDTA	Placebo
Stroke	1	0
Hypocalcaemic symptoms	6	2
Fatigue	12	11
Faintness	11	1
Gastrointestinal symptoms	11	7
Renal complications		
S-creatinine increase	7	9
Proteinuria	10	4
Phlebitis at infusion	35	28
Pain at infusion site	9	5
Headache	7	7
Raynaud's phenomenon	1	0
Metallic taste	1	0
Dermatitis	1	0

Discussion

This study did not demonstrate any effect of EDTA chelation therapy in the treatment of intermittent claudication. The walking distances (PWD and MWD) improved to the same extent in both groups. The A/I index remained unchanged throughout the study period, and no difference was found in the patients' subjective impression of the therapeutic result.

Two previous studies of the same target population demonstrated a 60% increase in walking distance in the placebo group over a 6-month period [20, 21]. This response has been ascribed to the development of collaterals as well as psychological factors, when patients with the same somatic problem are brought together, i.e. a placebo response.

We used 20 infusions of 3 g Na_2EDTA, a dosage and treatment regimen that is claimed to be effective. Olszewer *et al.* [19] used 10 infusions of 1.5 g Na_2EDTA and reported a considerable effect on IC. The attempted double-blind design of that study could not be achieved due to the dramatic effect in 50% of the 10 patients studied [19].

EDTA-chelation therapy in atherosclerosis is proposed to act by binding calcium and other cations, thus causing an increase in renal excretion of these metals. Lowering ionized calcium in serum mobilizes calcium from the atherosclerotic plaques, thus causing a reduction in atheromatous formations. Secondarily, EDTA is thought to relax vascular tone, inhibit platelet aggregation, lower LDL and VLDL, and act as a free-radical scavenger [18, 19]. However, Olszewer *et al.* [18] stated that these theories were purely speculative and based on empirical evidence.

In recent years, chelation therapy has been combined with large doses of vitamins and minerals according to the guidelines laid out by the American College for Advancement in Medicine (ACAM) [19]. Magnesium sulphate (Mg_2SO_4) is recommended as an adjuvant to reduce the pain at the infusion site, frequently experienced by patients receiving EDTA [16]. We did not add magnesium to the infusion, and observed the same incidence of local pains and phlebitis in the two groups. Thus the double-blind design of the study could be maintained without any problems. The low incidence of these side-effects is probably due to the fact that we used an isotonic solution, while in general hypo-osmolar solutions have been used. Furthermore, it has been stated that addition of magnesium should improve the therapeutic effect of EDTA [18]. However, the same beneficial effects on PVD have been reported by chelators using both Na_2EDTA [11–17] and $Na_2MgEDTA$ [18, 19]. In the absence of any reasons for adding magnesium supplements to the infusion, we preferred to administer it orally.

In conclusion, intraveneous EDTA treatment did not result in any improvement of intermittent claudication when compared to placebo. EDTA-chelation therapy does not have a potential role in the clinical therapy and management of peripheral vascular disease.

Acknowledgements

This study was supported by: The Danish Heart Foundation; The Medical Research Foundation for Region, 3 Denmark; Fru Olga Bryde Nielsen Fondation, Hillerød; Kaptajnløjtnant Harald Jensen og Hustru's Foundation, Hillerød; Else og Mogens Wedell-Wedellsborg Foundation; and the Danish Medical Research Council. The Multitabs® were issued by Ferrosan.

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Received 22 May 1991, accepted 13 August 1991.

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Am. J. Surg, Vol 162: 122-125, 1991

Arteriographic Findings in EDTA Chelation Therapy on Peripheral Arteriosclerosis*

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In a randomized, double-blind, controlled study, 153 patients with claudication were each given either 20 infusions of Na_2EDTA or 20 infusions of saline. Walking distances and ankle/brachial indices were measured before, during, and after treatment. In 30 patients, angiograms and transcutaneous oxygen tensions were obtained before, during, and after treatment. The patients' subjective evaluations of the effect of treatment were also recorded.

It is concluded that EDTA chelation therapy has no effect in patients with intermittent claudication in the legs caused by arteriosclerosis.

Etylenediaminetetraacetic acid (EDTA) chelation therapy of peripheral arterial disease has become a controversial issue in the Western Hemisphere over the last decade, and reports have been confined to the holistic literature. The results of randomized, double-blind, controlled studies have not yet been published.

The mechanism underlying the postulated effect of EDTA on arteriosclerotic disease is speculative, and scientific documentation in experimental models as well as in clinical trials is lacking.

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*This presentation is part of a study organized by The Danish Vascular Research Group who are listed in the appendix.

†The originators of the total multicenter project.

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Presented at the 19th Annual Meeting of the Society for Clinical Vascular Surgery, Kauai, Hawaii, April 3–6, 1991.

It is not realistic to prove—or rather disprove—the postulated effects of different types of alternative medicine, but EDTA treatment is given by members of the medical profession, and many patients with arteriosclerosis in coronary or peripheral arteries spend thousands of dollars on this treatment hoping for a cure.

For these reasons, vascular surgeons are obliged to study EDTA chelation therapy in scientific trials in order to have the data needed to advise the population in general and patients with claudication in particular on the indications, efficacy, and side effects of this treatment.

PATIENTS AND METHODS

A total of 153 patients with stable, intermittent claudication with a walking range of 50 to 200 m and an ankle/brachial index below 0.8 were included in the study. All patients were more than 40 years of age. Exclusion criteria are listed in **Table I.**

The trial was designed as a randomized, double-blind study. One group of patients received Na_2EDTA 3 g and NaCl 8.4 g in sterile water added to 1,000 mL of isotonic solution; the other group received 1,000 mL of isotonic saline. The randomization was performed by each center in blocks of 10 according to a randomization code. All patients received oral vitamins, trace elements, and mineral supplements, i.e., vitamin A, vitamin B_1, vitamin B_2, vitamin B_6, vitamin B_{12}, folic acid, nicotinamide, pantothenic acid, vitamin C, vitamin D, vitamin E, magnesium, iron, zinc, copper, iodine, manganese, chromium, selenium, and molybdenum.

Before entering the trial, all patients had a physical examination and a number of laboratory tests, including determination of coagulation status, blood glucose level, and liver and kidney function. Patients were instructed to stop smoking, to lose weight (if applicable), and to increase their physical training.

Each infusion lasted for 3 to 4 hours and took place in the outpatient clinic. A total of 20 infusions were given to each patient over a period of 6 to 10 weeks.

Treadmill tests, plethysmography, and laboratory tests were performed at the beginning of the trial. After 10 and after 20 infusions, laboratory tests were repeated and the following parameters were measured: (1) walking distance on a 10° ascending climb at a pace of 3.6 km/hour before, halfway, after the last infusion, and at 3 months of follow-up; (2) distal segmental systolic blood pressures before and after treatment (as assessed by strain gauge pletysmography); (3) digital subtraction angiograms before and after treatment in a subgroup of 30 patients; and (4) transcutaneous tension of oxygen diffusion on the skin above the anterior tibial compartment measured on a horizontal and an elevated extremity, respectively.

This report focuses on the subgroup of 30 patients from the Department of Vascular Surgery in Aarhus. All patients except one in this group smoked. Comprehensive analyses of the entire data will be published elsewhere.

RESULTS

The maximal walking distances before treatment, after 10 infusions, and after 3 months of follow-up are shown in **Figure 1.** The improvement in both groups during the first half of the treatment period reflects the well-known phenomenon of spontaneous improvement. After 10 infusions and after 3 months of follow-up, there was no further improvement and no significant differences between the two groups.

The ankle/brachial indices before treatment, after 7 infusions, after 14 infusions, after a total of 20 infusions, and after 3 months of follow-up are shown in **Figure 2.** The curves are horizontal and are not significantly different.

The arteriograms were assessed before and after treatment with the evaluator "blinded" to the patient's treatment (**Table II**). Twenty-eight of 30 arteriograms were unchanged or worse, with only 2 showing improvement. There was no pattern in the evaluation suggesting that EDTA had a curative effect on the arteriosclerotic disease.

The transcutaneous oxygen tensions before and after treatment at horizontal and elevated levels are shown in **Figures 3** and **4.** Again, there were no significant differences between the two groups.

The patients' evaluations of their treatment were also performed "blindly." As can be seen from **Figure 5**, there was no difference between the two groups.

The results of laboratory tests on entry were within the normal range. No changes in these parameters were observed during the study period.

Side effects of treatment were nonspecific and there was no difference between the two groups. The incidence of phlebitis at the site of infusion was similar in the two groups.

COMMENTS

Vascular surgeons use conservative medical therapy to treat peripheral arterial insufficiency caused by arteriosclerosis if patients are not motivated or are not suitable candidates for surgery.

The goals of conservative treatment are to improve the collateral circulation, avoid the adverse effects of nicotine and carbon monoxide, and minimize the weight load on the legs if applicable.

For the past few decades, EDTA chelation therapy of peripheral vascular disease has been one type of alternative treatment that supporters have claimed not only relieves symptoms but even cures the arteriosclerotic disease. If this were true, it would have major worldwide implications.

To date, a substantial number of reports have been published in the holistic literature, but none of these have met scientific criteria, and the theoretic mechanism for the postulated effect of EDTA is purely speculative. As far as we know, this is the first randomized, double-blind, controlled study addressing this highly controversial issue.

In this study, the walking distance improved equally in both groups during the first 10 infusions, reflecting the well-known placebo effect. After this, the walking distances were similar. The ankle-brachial indices were constant in both groups during the study period. The angio-

TABLE I

Exclusion Criteria

Vascular surgery within the last 12 months
Ischemic rest pain or gangrene
Moderate or severe venous insufficiency
Renal insufficiency
Diabetes mellitus
Thyroid and parathyroid disorders
Hepatic dysfunction
Significant cardiopulmonary failure (e.g., acute myocardial infarction within the last year)
Coexistent carcinomas
Tuberculosis within the last year
Pregnancy
Other conditions that could limit the patient's walking distance or the full understanding of the study
Patients receiving anticoagulants, nitroglycerin, or lithium
EDTA chelation therapy within the last 24 months

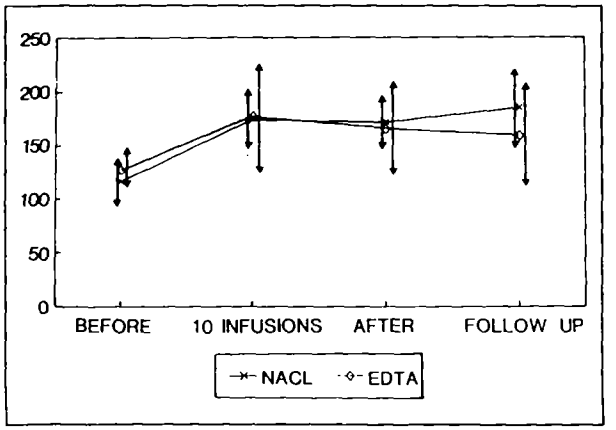

Figure 1. Walking distance in meters before treatment and after 10 and 20 infusions and at follow-up after 3 months.

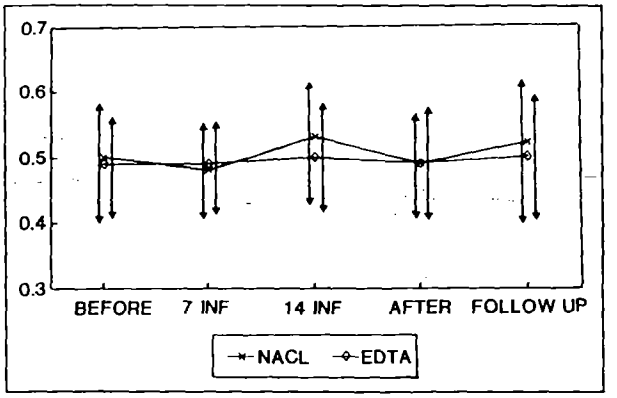

Figure 2. Ankle/brachial index before treatment and after 7, 14, and 20 infusions and at follow-up after 3 months.

TABLE II
Evaluation of Angiograms Before and After Treatment

	Unchanged	Worse*	Better	Total
Aorto-iliac	28	2 (2)	0	30
Right femoral	29	1 (1)	0	30
Left femoral	29	1 (1)	0	30
Right crural	25	4 (4)	1	30
Left crural	21	7 (5)	2 (1)	30

*Numbers in parentheses indicate number of patients treated with Na_2EDTA.

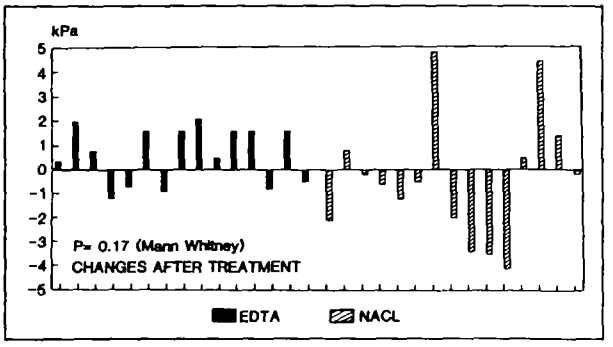

Figure 3. Changes in transcutaneous oxygen tension at horizontal level after treatment.

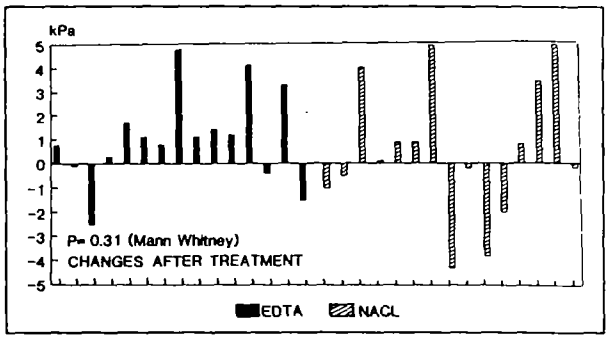

Figure 4. Changes in transcutaneous oxygen tension at elevated level after treatment.

grams did not suggest a beneficial effect of EDTA. The oxygen tensions in the skin over the anterior tibial compartment measured on a horizontal and on an elevated extremity were not significantly different between the two groups, and there was no significant difference between the two groups concerning the patients' own evaluations of the effect of treatment.

We conclude that EDTA chelation therapy has no beneficial effect on objective parameters or on subjective evaluations in patients with claudication in the lower extremities caused by arteriosclerosis.

As mentioned, these data are based on a subgroup of 30 patients from Aarhus, which is part of a multicenter study. Our specific interest in this subgroup of patients is in recording angiographic findings and oxygen tension measurements before and after treatment. The results in this study are identical with the results in the total multicenter study as to walking distances and distal segmental systolic pressures.

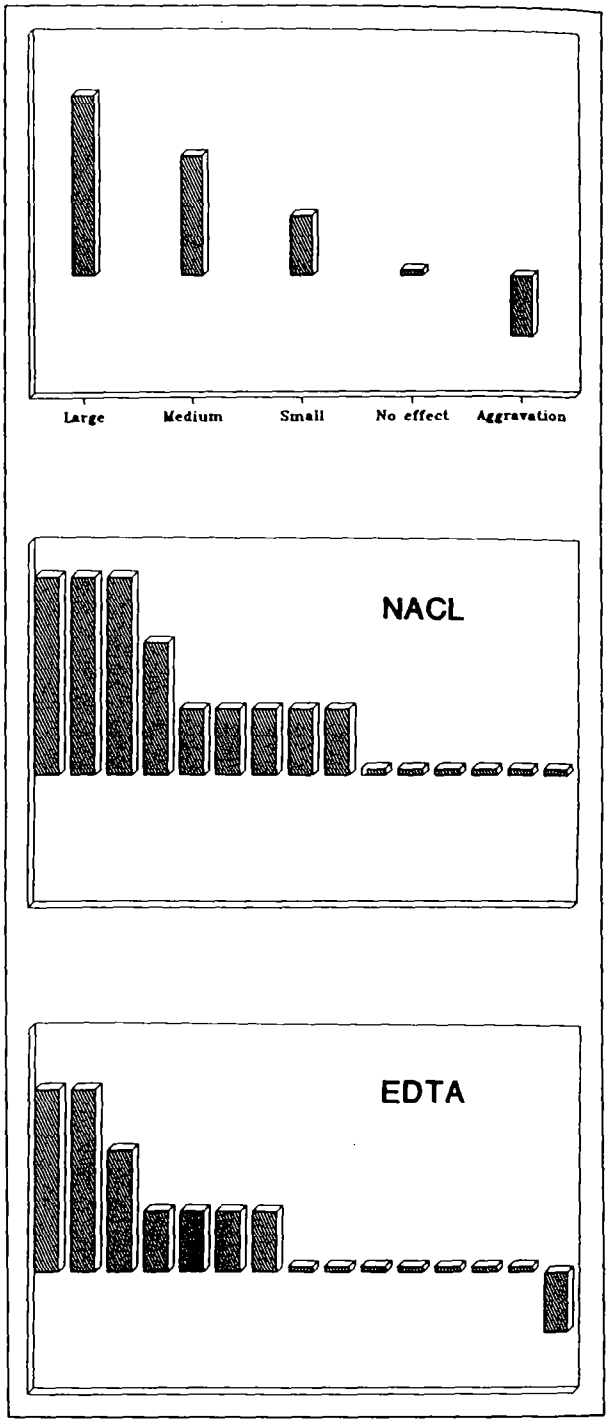

Figure 5. Patients' evaluations of the effect of treatment.

APPENDIX

The Danish Vascular Research Group includes Bernadette Guldager, MD, Svend Juul Jørgensen, MD, Svend Ottesen, MD, Department of Surgery, Hillerød; Rolf Jelnes, MD, Anette Klaerke, MD, Department of Vascular Surgery, Alborg; Jørgen Sloth-Nielsen, MD,

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DISCUSSION

Dr. Kerstein: I know of 16 patients treated with EDTA by physicians whose training was not in internal medicine or vascular surgery. These patients each paid $5,000 to $10,000 for treatment, and three returned to our clinic with renal failure. The other patients were the same or worse after treatment. Did you observe renal failure as a result of EDTA treatment?

Dr. Mouritzen: I think renal failure is related to the dose of EDTA used, and we used a dose designed not to result in renal dysfunction. We undertook this study because politicians in Denmark were debating whether EDTA treatment should be included under Danish Medicare. If approved, millions of dollars would be spent on a useless treatment. The politicians wanted a scientific study performed to investigate the efficacy of EDTA treatment, and the government funded the work.

Dr. Mellick: We had six people in our area die of myocardial infarction during or after EDTA treatment. Did you find this effect?

Dr. Mouritzen: No, I think in any group of arteriosclerotic patients, myocardial infarctions will occur.

Dr. Strandnes: We had a similar experience in trying to halt the use of chelation in Washington state. Although the judge agreed with our position, he said he needed data from an objective study. The National Institutes of Health, however, refused to fund a study of what they consider an unethical procedure. I believe, Dr. Mellick, that Australia has initiated a study of EDTA therapy, and with this study, perhaps we can prevent the use of this treatment.

Circulation Vol. 90(3) 1194-1199 1994

Chelation Therapy for Intermittent Claudication

A Double-Blind, Randomized, Controlled Trial

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Background The use of repeated intravenous infusions of EDTA, which has become known as "chelation therapy," has been promoted for treating intermittent claudication as well as a wide range of other disorders. Multiple reports of excellent results in large numbers of patients have encouraged the use of this regimen. The lack of well-controlled studies substantiating the benefits of this treatment has limited its use mainly to private clinics. The aim of the study was to assess the benefits of chelation therapy in patients with intermittent claudication.

Methods and Results A double-blind, randomized, controlled trial included 32 patients with intermittent claudication who were randomized to a treatment group (15) and a control group (17). Main outcome measures were subjective and measured walking distances and ankle/brachial pulse indices. Other outcome measures included lifestyle and subjective parameters of improvement, cardiac function, ECG, renal function, hematology, blood glucose, and lipid biochemistry. No clinically significant differences in main outcome measures between chelation therapy and placebo groups were detected up to 3 months after treatment. Measures of mood state, activities of daily living, and quality of life factors were not consistently affected by chelation therapy. An equal proportion (13%) of each group thought that they had received the active agent. The proportion of patients showing an improvement in walking distance was not significantly different between the chelation group (60%) and the control group (59%).

Conclusions Chelation therapy has no significant beneficial effects over placebo in patients with intermittent claudication. (*Circulation*. 1994;90:1194-1199.)

Key Words • atherosclerosis • peripheral vascular disease • lifestyle

Chelation therapy, a program of repeated intravenous administration of ethylenediaminetetraacetic acid (EDTA) together with vitamin supplementation, has been promoted as an effective treatment for a wide range of clinical conditions.[1-3] In atherosclerotic and specifically peripheral vascular disease, very marked benefits have been reported.[4,5] Despite the considerable enthusiasm of the proponents of chelation therapy, there has been a notable lack of acceptance of its use by the majority of medical practitioners for conditions other than heavy metal poisoning.[6,7] This has lead to a long-standing debate in the medical literature, the press, and the political arena about the efficacy of, the access to, and the funding for this treatment in a number of countries.[7-13] Numerous clinics dedicated to this therapy have been established, but state funding has not been forthcoming.

EDTA has many biochemical effects, including chelation of calcium and other divalent ions, free radical scavenging, inhibition of lipid peroxidation, cell membrane stabilization, and calcium channel blockade.[14-16] These effects of EDTA have given broad scope to the possible reasons why chelation therapy should have a clinical benefit. Plausible as these hypotheses may be, they lack the supportive evidence of relevant in vivo experiments and appropriately designed clinical trials. Many claims for the efficacy of chelation therapy have been based on uncontrolled studies, although some of these have included substantial numbers of patients[3] (L.T. Chappell and J.P. Stahl, unpublished data, 1993).

A small double-blind trial in 1990 reported significant success with chelation therapy in a group of patients with peripheral vascular disease.[17] Subsequently, a larger multicenter study published in 1991 failed to demonstrate a benefit.[18,19] Aspects of this study have been criticized by proponents of chelation therapy.[20] We now report a single-center, double-blind, randomized, controlled trial in a group of patients with intermittent claudication.

Methods

Patients who had been fully investigated for intermittent claudication were recruited from the Dunedin Hospital peripheral vascular disease clinic. Participation in the trial was offered to patients with peripheral atherosclerotic disease, which was confirmed by arteriography, for whom other invasive interventions were not indicated. Patients were required to have no other debilitating disease affecting walking, to be greater than 45 years of age, to be nondiabetic, and to have no significant renal disease. All patients were counseled to anticipate a positive effect of chelation therapy, and they received the promotional literature usually provided by chelation therapy clinics.[21] Appropriate dietary recommendations and a requirement to stop smoking were made.

The study received ethical approval, and patients were required to give written informed consent before being included. A requirement for entry into the trial was a variation of less than 20% in measured walking distance in three consecutive noninvasive vascular laboratory assessments, performed on different days. Further workup and subsequent observations included segmental pressure and pulse volume plethysmography and femoral and posterior tibial artery pulsatility indices.[22] These were measured at rest and after

Received March 21, 1994; revision accepted May 9, 1994.

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exercise on a treadmill at 4 km/h and 10% gradient. Lower-limb skin blood flow and transcutaneous oxygen tensions were measured.[23,24]

Levels of cardiac function were monitored during a modified Bruce exercise test[25] in the cardiology department. Plasma lipid, lipid peroxides, and oxidized low-density lipoprotein levels were measured.[26]

The effects of chelation therapy on behavior and attitudes related to lifestyle were investigated by means of previously validated, self-administered questionnaires. The following were included: the main instrument from the Life in New Zealand National Survey, which included questions on physical activity, perceived fitness, smoking, alcohol consumption, and dietary practices in the previous 4 weeks[27]; the 12-item form of the General Health Questionnaire, which assessed anxiety-depression in the previous 4 weeks[28]; and the Profile of Mood States, which measured feelings of tension, anger, depression, confusion, fatigue, and vigor in the previous 2 days.[29] In addition, several questions making use of visual analogue scales were devised to gauge patients' global feelings of well-being and the effect of poor circulation on their social and private leisure activities. All questions were assembled into one booklet and were completed twice before treatment and then once at each of the assessment stages. The patients' perception of the treatment group to which they were assigned was assessed by means of a questionnaire after the 3-month visit.

Patients were randomized in blocks of 10, and preparation of the assigned infusions was conducted independently by the hospital pharmacist. The 500-mL infusion for the active treatment group was pharmaceutically prepared and contained 3.0 g disodium EDTA, 0.76 g magnesium chloride, and 0.84 g sodium bicarbonate in normal saline. The placebo was an intravenous infusion of 500 mL normal saline. In addition, both groups received Parentrovite (thiamine hydrochloride 250 mg, riboflavine phosphate [sodium salt] 5.5 mg, pyridoxine hydrochloride 50 mg, ascorbic acid [sodium salt] 500 mg, nicotinamide 160 mg, sodium pantothenate 5 mg, glucose anhydrous 1000 mg, sodium metabisulphite 4 mg) in each infusion. The infusions were indistinguishable by container, labeling, or color. Each patient received a total of 20 infusions, each given over 3 to 3.5 hours, twice per week for 10 weeks. Daily oral supplements of vitamins as recommended by the American Academy of Medical Preventics and American Board of Chelation Therapy[30] were given throughout the period of treatment. Urinalysis, standard hematology, renal function, and serum calcium, zinc, magnesium, and iron levels were measured weekly and at follow-up assessments to monitor for the possible toxic side effects of chelation therapy.[31] Patients were supervised throughout the duration of each infusion with hourly pulse and blood pressure monitoring. Patient assessments and data analyses were carried out by different staff groups who worked independently and were blind to the identity of the treatment and control groups.

The major end points for the study were: measured walking distances, defined as the total distance the patient was able to walk at 4 km/h on a treadmill at 10% gradient (1) to onset of pain and (2) before stopping because of disabling claudication; subjective walking distance, defined as the distance the patients considered they were able to walk before stopping because of claudication; and ankle/brachial indices (ABI) measured at rest and immediately after the treadmill exercise.

The sample size required for the study was calculated from an algorithm that combined retest reliability of outcome measures, type I error rate, and power to detect a minimum difference in effect size (Δmean/SD) between treatment and control groups. Retest of the first 20 patients entering the study gave reliability correlations of 0.98 and 0.96 for the outcome measures of absolute walking distance and ABI, respectively. With the usual assumptions of 80% power and type I error of 5%, these reliabilities implied that a controlled trial involving at least 30 patients would detect effect-size differences of 0.2 for walking distance and 0.3 for ABI. Such effect sizes are regarded as small on theoretical grounds.[32] They equate with differences in improvement in walking distance and ABI of approximately 10% and 5%, respectively, which are less than what is usually regarded as clinically significant and also far less than the improvements that have been claimed for chelation therapy (for walking distance, 100% to 400% in 90% of patients[3,17]; for ABI, up to 86% in 93% of patients[4]).

Assessments after entry into the trial were carried out after 10 infusions, at the completion of treatments, and at 3, 6, and 12 months after treatment. The code was broken when the required number of patients had completed the 3-month posttreatment assessment, but only after the statistical analysis had been performed. The results up to this time are presented here. The 6- and 12-month assessments are still in progress.

Data were analyzed with the Statistical Analysis System (SAS Institute). The significance of differences in effects between the chelation and control groups, and any overall changes in both groups with time, was tested with repeated-measures ANOVA. Walking distances were log transformed and other variables not normally distributed were rank transformed to reduce effects of heteroscedasticity and skewness on subsequent analyses. Bilateral measures of peripheral vascular disease were grouped by better and worse limbs as determined by the postexercise pulse index before infusions. Effect sizes were calculated to standardize comparison of changes in mean values of variables following treatment; magnitudes of effect size were interpreted according to the criteria of Cohen.[32] Continuity-adjusted χ^2 tests were performed to test the significance of the difference of frequency of improvement in each group. The type I error rate for declaring statistical significance was set to 0.05.

Results

Of the 59 patients invited to enter the trial, 32 met the repeated assessment criteria for inclusion, agreed to take part, and completed treatment. Exclusions made before infusions were due to inconsistent walking distances (9), rest pain (2), cardiac disease limiting exer-

TABLE 1. Characteristics of Chelation and Control Groups at Start of Trial

Parameter	Chelation	Control
No. of subjects	15	17
Age, y	67.7±7.0	66.9±6.7
Sex		
Male	13	15
Female	2	2
Duration of intermittent claudication, y	3.6±2.7	3.9±2.7
Smokers, %	86	82
Previous myocardial infarcts or strokes, %	20	24
Previous vascular surgery, %	20	24
Previous lower-limb angioplasty, %	26	29
Weight, kg	71.8±10.5	77.9±12.7
Height, m	1.71±0.08	1.69±0.09
Body mass index	24.5±3.7	27.1±3.3*
Cholesterol, mmol/L	6.22±1.04	6.97±1.62

Data are mean±1 SD where appropriate.
*Significant difference from chelation group ($P<.05$).

TABLE 2. Main Outcome Measures at Various Stages of the Trial Comparing the Chelation and Control Groups

Parameter	Group	Screening	End of Treatment	3 Months After Treatment
ABI (exercise), better leg	Chelation	0.55±0.24	0.58±0.30	0.58±0.28
	Control	0.61±0.32	0.61±0.32	0.67±0.34
ABI (exercise), worse leg	Chelation	0.31±0.16	0.32±0.18	0.34±0.18
	Control	0.32±0.14	0.34±0.17	0.32±0.17
ABI (resting), better leg	Chelation	0.74±0.16	0.76±0.2	0.78±0.12
	Control	0.75±0.19	0.86±0.36	0.73±0.21*
ABI (resting), worse leg	Chelation	0.59±0.13	0.70±0.36	0.62±0.15
	Control	0.61±0.11	0.60±0.15	0.58±0.13*
Measured WD, m	Chelation	185±117	208±135	233±138
	Control	196±121	223±149	230±195
Measured WD to onset of pain, m	Chelation	92±64	101±50	104±62
	Control	98±67	121±89†	123±108†
Subjective WD, m	Chelation	170±213	413±775	448±556
	Control	182±115	327±461†	381±473†

ABI indicates ankle/brachial index; WD, walking distance.
*Significant changes between groups ($P<.05$).
†Significant overall effect for both groups combined ($P<.05$).

cise tolerance (4), detection of impaired renal function or diabetes (4), intercurrent illness (2), and unavailability to participate in the full protocol (6). Characteristics of the patients in the chelation and control groups are shown in Table 1.

There was a significant improvement in the walking distances in both groups at the end of the infusion program. However, the major end points of improved absolute and subjective walking distances as well as postexercise ABI were not significantly different in the two groups at any time during treatment or follow-up (Table 2). Changes in skin blood flow, transcutaneous oxygen, and pulse volume recordings before and after exercise were also not significantly different between the groups immediately after treatment (Fig 1) or at the later assessment.

At 3 months after treatment, resting ABI of both the better and worse legs showed some improvement in the chelation group (Table 2). A clinically significant improvement of at least 0.1 in the resting ABI of the worse leg was observed in two patients in each group. The femoral pulsatility index (normal range, 6 to 15) in the worse leg had improved from 3.3±0.9 to 4.2±1.2 in the chelation group and decreased from 4.1±0.8 to 3.6±0.9 in the control group ($P<.01$). Similar trends were noted in the femoral artery of the better leg and in the posterior tibial arteries, but these did not reach statistical significance. No other parameters of peripheral vascular function differed at 3 months, and the percentage of patients that showed any increase in walking distance at this assessment was 60% and 59% for the chelation and control groups, respectively.

Changes in lifestyle parameters at the end of the treatment period were not significantly different between the two groups. The measure of tension increased in the control group and decreased in the chelation group, an effect that was no longer evident at 3 months.

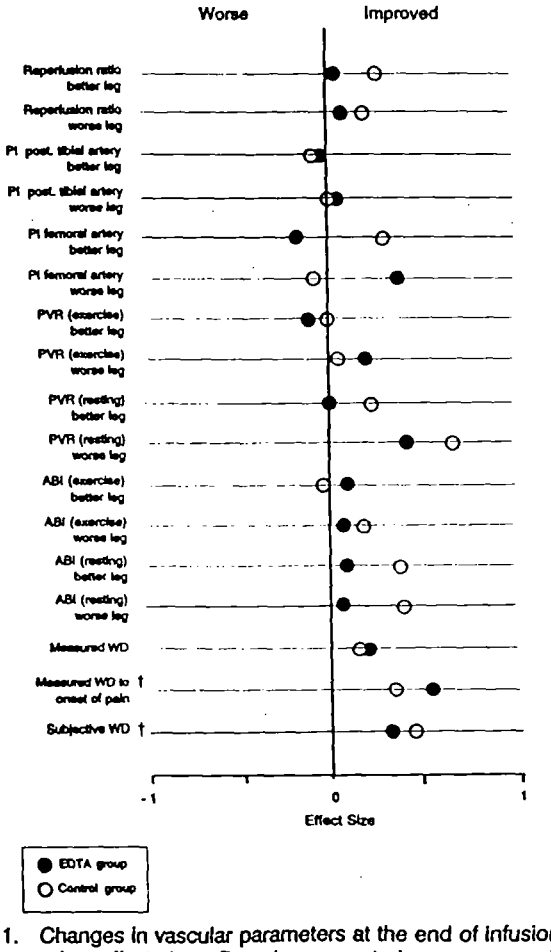

FIG 1. Changes in vascular parameters at the end of infusions expressed as effect sizes. Based on repeated-measures analysis, no changes between the two groups were significant, but differences immediately after the infusion period are indicated (†$P<.05$). PI indicates pulsatility index; PVR, pulse volume recording; ABI, ankle/brachial index; and WD, walking distance.

TABLE 3. Lifestyle Measures at Various Stages of the Trial Comparing the Chelation and Control Groups

Parameter	Group	Pretreatment	End of Treatment	3 Months After Treatment
Effect of poor circulation†				
Private	Chelation	3.4±2.2	4.3±2.3	4.3±2.7
	Control	4.9±2.4	3.9±2.4	5.1±2.1
Social	Chelation	4.1±2.7	4.1±2.3	4.0±2.4
	Control	4.8±2.5	4.8±2.6	4.3±2.3
Home	Chelation	3.8±2.7	4.8±2.4	3.7±2.6
	Control	4.1±2.4	3.4±2.3	4.1±1.8
Work	Chelation	5.1±2.3	5.4±1.9	5.1±2.1
	Control	5.1±2.4	4.7±2.5	5.1±2.2
Profile of mood state‡				
Anger	Chelation	5.6±6.4	5.9±4.9	8.4±6.7
	Control	7.6±8.8	6.5±8.5	7.0±10.4
Tension	Chelation	24.2±19.1	16.1±11.8	18.7±16.0
	Control	18.6±15.6	19.6±16.4*	18.2±19.5
Depression	Chelation	9.4±13.6	7.1±11.8	9.3±13.4
	Control	7.6±11.2	7.8±10.3	6.9±11.5
Confusion	Chelation	18.3±15.8	17.4±16.8	20.7±11.5
	Control	18.3±13.9	14.9±11.2	15.9±11.1
Vigor	Chelation	51.2±18.4	42.5±17.1	48.9±18.5
	Control	46.0±22.0	47.5±19.0	44.5±17.0
Fatigue	Chelation	22.3±16.7	20.2±12.6	24.2±14.9
	Control	23.1±26.9	21.9±23.2	22.8±22.7
Level of physical activity				
Moderate	Chelation	19.8±10.3	22.0±9.7	26.3±13.5*
	Control	40.6±26.5	34.0±23.7	35.9±22.7
Relative to self§	Chelation	2.7±0.7	3.5±0.8	3.4±0.9*
	Control	2.7±0.8	2.7±0.4	2.9±0.9
Relative to others (mild)‖	Chelation	3.3±1.1	3.9±0.9	3.6±1.3
	Control	3.8±1.4	3.8±1.6	3.8±1.4
Relative to others (strenuous)¶	Chelation	2.4±1.2	3.0±1.6	3.0±1.3
	Control	3.0±1.6	3.4±1.7	2.8±1.3
Other parameters				
General Health Questionnaire‡	Chelation	19±16	17±17	20±23
	Control	20±15	20±14	17±17
Perceived fitness‡	Chelation	21±12	26±12	28±11
	Control	19±13	22±14	24±17
Perceived well-being¶	Chelation	6.5±2.2	6.0±1.6	5.7±2.3
	Control	6.6±2.8	6.6±1.7	5.9±1.7
Perceived life quality¶	Chelation	6.7±1.5	6.5±1.2	5.6±1.9
	Control	6.4±2.5	6.1±1.9	5.9±1.9

*Significant difference between groups ($P<.05$).
†Scores on visual analogue scale: 0 (no effect) to 10 (very severe).
‡Percent of maximum possible score.
§Score on 5-point scale: 1 (much less) to 5 (much more).
‖Score on 7-point scale: 1 (very much less) to 7 (very much more).
¶Score on visual analogue scale: 0 (worst) to 10 (best).

As shown in Table 3, at 3 months the levels of usual activity and low-intensity and mild-to-moderate exercise had all improved in the chelation group. The effect sizes for these changes were moderate (Fig 2). Chelation therapy had no benefit at this time on assessed levels of fatigue, physical well-being, mood, general quality of life, or on the specific effect of arterial disease on quality of life, work, home management, and social or private leisure activities.

There were no significant differences between the groups in patients' knowledge of the nature of their infusions: 12.5% of both groups thought that they had received chelation therapy; 68% of the placebo group and 50% of the treatment group thought they had received the placebo; the remaining patients were unsure which treatment they had received. There were no complications or withdrawals from the study in either group up to the 3-month assessment.

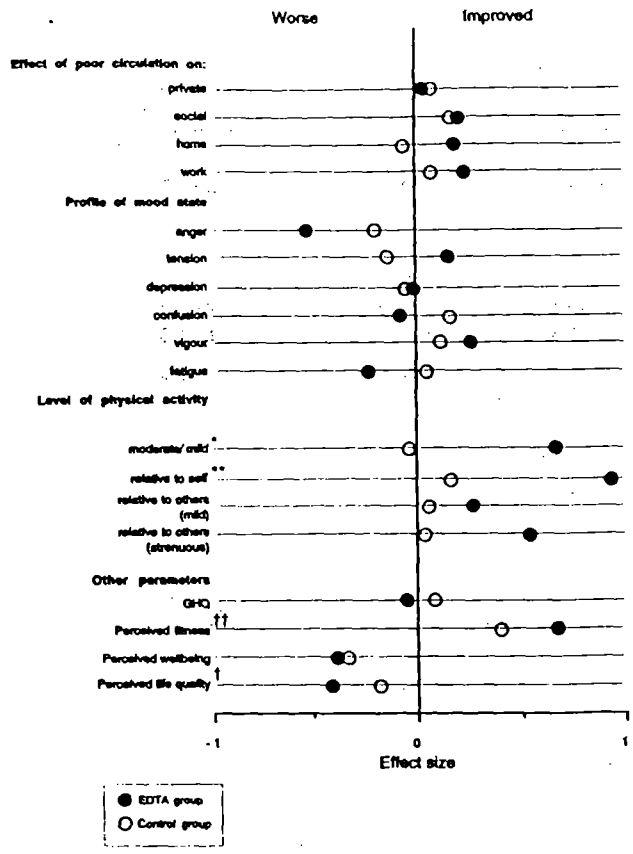

FIG 2. Changes in lifestyle parameters at 3 months after infusions expressed as effect sizes. Significant differences between groups (*$P<.05$, **$P<.01$) and significant changes from pretreatment for both groups combined (†$P<.05$, ††$P<.01$) are indicated.

Discussion

After 10 weeks of treatment, chelation therapy provided no immediate benefit on peripheral vascular hemodynamics, functional measures of activity, lifestyle, quality of life, or perceptions of health related to peripheral vascular disease when compared with a control group. Particularly for the major end points of walking distances and postexercise ABI, this study had the power to demonstrate whether this therapy was as effective as reported. It appears that chelation therapy does not provide that benefit for patients with peripheral vascular disease.

One of the difficulties in assessing the benefit of therapy for peripheral vascular disease is the well-recognized improvement in walking distances achieved with conservative management. The improvement in the chelation group if viewed alone could readily, but mistakenly, have been attributed to the EDTA. This highlights the necessity of controlled studies for evaluation of therapies for intermittent claudication.

Additional benefits 3 or more months after chelation have been claimed (M.E. Godfrey, personal communication, 1992). Therefore, it was important to carry out follow-up well after treatment was completed. In this study, no more clinically significant late benefits were seen in the chelation group than were observed in the control group. Most of the peripheral hemodynamic measures remained indistinguishable, and there were no detectable benefits in quality of life or in most of the activities of daily living. At this time, the patients were also unable to distinguish the therapy that they thought they had received.

However, there was an interesting small improvement in the resting ABI and femoral artery pulsatility indices observed 3 months after chelation. Whether these are in any way related to the moderate treatment effect size noted in some levels of activity at this stage remains unclear. The reliability of outcome measurements in the study certainly had the power to detect benefits much smaller than those claimed for chelation. The significance of these positive late findings will require further study.

A relatively unique aspect of this study has been the concurrent evaluation of the patients' mood state, lifestyle, diet, and activities of daily living and their perceptions of the influence of the treatment on these factors. In view of the wide range of actions put forward by which chelation could possibly improve patient response, these assessments were considered to be particularly important. For example, changes in muscle metabolism or mood state could well modify the performance and perception of activities of daily living without direct changes in hemodynamic function. No such alternative benefits were identified. Differences in dietary food items and quantities as well as cooking habits and alcohol consumption during the study period were also excluded. The effect on lipid metabolism and cardiac function as well as follow-up after 1 year will be reported subsequently.

Whereas there is a general consensus for the protocol for the administration of chelation therapy, there is also still some minor diversity of practice. The study tested the essential component of the therapy (EDTA) in an appropriate formulation and amount and with strict blinding. The specific regimens of vitamin supplementation, dietary advice, and general support given to all the subjects should not be relevant to the comparative outcome. The previous encouraging reports of chelation therapy for the treatment of intermittent claudication have not been substantiated by this study.

Acknowledgments

This study was supported by a grant from the National Heart Foundation of New Zealand. We gratefully acknowledge the technical support of E.A. Smith, R.A. Christie, J.A. Smiley, and A.R. Patterson.

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Chelation Therapy for Intermittent Claudication

Guldager B, Jelnes R, Jørgensen SJ, et al. EDTA treatment of intermittent claudication—a double-blind, placebo-controlled study. J Intern Med. 1992 Mar;231:261–7.

Objective
To assess the effectiveness and safety of chelation therapy with ethylenediamine-tetraacetic acid (EDTA) for patients with stable intermittent claudication.

Design
Randomized, double-blind, placebo-controlled trial with 6-month follow-up after therapy.

Setting
7 departments of vascular surgery in Denmark.

Patients
56 women and 103 men > 40 years of age, with stable intermittent claudication for a duration ≥ 12 months; a pain-free walking distance of 50 to 200 m on a treadmill at 3.6 km/h, with an inclination of 10°; and ankle/brachial blood pressure index < 0.8 in the worse leg. 69% of patients were smokers. Patients with recent changes in medication, serious illness, or contraindications to EDTA were excluded. 3-month and 6-month follow-up was 94% and 77% complete, respectively.

Intervention
Patients were randomized to 20 intravenous infusions of Na_2EDTA, 3 g, and NaCl, 8.4 g, diluted in 1 L H_2O ($n = 80$), or to placebo solution ($n = 79$). The duration of each treatment was 3 to 4 hours. Treatment took 5 to 9 weeks. Vitamins, trace elements, and mineral supplements were given as 1 tablet daily during the treatment period. Patients were given advice on diet, smoking cessation, and exercise 153 patients completed the treatment period

Main outcome measures
Pain-free and maximal walking distances; ankle/brachial blood pressure index; patients' subjective ratings of effectiveness.

Main results
Walking distances improved similarly over 6 months for both groups of patients: Mean (SD) pain-free walking distance increased from 74 (25) m to 97 (47) m for the EDTA group compared with 82 (36) m to 119 (93) m for the placebo group. For all comparisons of pain-free and maximum walking distances between patient groups during the treatment period and follow-up, the ratio of percent change was between 0.91 and 1.04, and neither group was consistently superior to the other. The groups did not differ in ankle/brachial index. Patients in both groups evaluated their treatment similarly, with approximately 50% noting some improvement. The groups did not differ during treatment in hypocalcemic symptoms, gastrointestinal symptoms, renal complications, or phlebitis.

Conclusion
EDTA chelation therapy was not more effective than placebo in treating intermittent claudication.

Sources of funding: Danish Heart Foundation; Medical Research Foundation for Region 3, Denmark; Fru Olga Bryde Nielsen Foundation; Kaptajnløjtnant Harald Jensen og Hustru's Foundation; Else og Mogens Wedell-Wedellsborg Foundation; Danish Medical Research Council.

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Commentary

This article is important because it may be the first scientific study of chelation therapy for atherosclerosis. The therapy was administered in a manner consistent with the recommendations of those who support chelation therapy, and the effectiveness of the therapy was objectively measured in a credible way. Those who believe in EDTA therapy will be confounded by the study, which proves the need for properly controlled trials to assess efficacy of this therapy. The 45% improvement in treadmill walking time on placebo is consistent with observations in studies comparing placebo with other treatments such as pentoxifylline.

A study design that I would recommend to investigators is the sequential crossover study because it minimizes the extent to which patients would be denied any benefit of treatment (1). In such a trial, if the therapy is effective, all patients would be on or have had the therapy at the end of 1 crossover.

The results of the study by Guldager and colleagues do not preclude a small benefit in intermittent claudication, nor do they preclude a benefit in stasis ulcers, dry gangrene, or other manifestations of atherosclerosis. There is, however, no evidence of such benefits. Thus, the practice and policy implications of this article are that previous recommendations by such bodies as the American Heart Association should stand: Treatment of atherosclerosis by infusion of chelating agents such as EDTA is of unproven benefit, with known toxicity (2, 3). They should be used only in the setting of properly controlled clinical trials.

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Victoria Hospital
London, Ontario

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REVIEW ARTICLE

SO MUCH WRITING, SO LITTLE SCIENCE: A REVIEW OF 37 YEARS OF LITERATURE ON EDETATE SODIUM CHELATION THERAPY

Michael T. Grier and David G. Meyers

OBJECTIVE: To determine the safety and efficacy of edetate sodium (ethylenediamine tetraacetic acid; EDTA) chelation therapy for atherosclerosis.

METHODS: Literature search using MEDLINE, encompassing 1966 through May 1993. Further references were obtained from articles and books, and from citations obtained from the American Academy of Medical Preventics.

RESULTS: 16 case reports or case series, 2 longitudinal studies, and 3 clinical trials were reviewed, along with testimonials cited in 19 books.

CONCLUSIONS: Little valid scientific evidence is available. Although the postulated mechanisms of action for EDTA are biologically plausible and EDTA appears to be safe, it has not been proven effective. Indeed, the best evidence shows it to be ineffective. Therefore, EDTA chelation therapy should not be used in clinical practice to treat atherosclerosis.

Ann Pharmacother 1993;27:1504-9.

TREATMENT OF atherosclerotic cardiovascular disease with edetate sodium (ethylenediamine tetraacetic acid; EDTA) chelation therapy was introduced in 1955.[1] It is estimated that more than 500 000 people are treated with EDTA chelation therapy each year.[2] Almost as many patients have been treated with this therapy as have been treated with coronary artery bypass surgery.[3]

Proponents of chelation therapy, including the American Academy of Medical Preventics, the American Board of Chelation Therapy, the American College for Advancement in Medicine, and the American Holistic Medical Association, contend that chelation therapy is highly effective. As stated by one author, "The plain and undeniable fact is that people are dying from atherosclerosis in part because of a lack of chelation therapy acceptance."[4] A physician who uses EDTA chelation therapy remarked, "This has nothing to do with science; this is a financial fight, pure and simple. If science were the issue, bypass surgery would be illegal. In spite of obvious benefits to heart patients, EDTA fell into disfavor in the mid-1960s for two reasons: First, the lucrative surgical approach to heart and vessel disease was on the rise. Second, the patent on EDTA held by Abbott Laboratories had expired, so the drug company had no incentive to study EDTA or to promote its use....EDTA almost died for lack of a vested interest."[5]

The opposing view was outlined in the *Journal of the American Medical Association*. "The Department of Health and Human Services released a report entitled *EDTA Chelation Therapy for Atherosclerosis* in 1981 (HRST Assessment Report Series Volume, No. 18). It noted that chelation for this indication is controversial, that there is no accepted rationale for its effectiveness, and that its safety is questioned. *The Medical Letter*, in 1982, reviewed the experience over 20 years and concluded that 'There is no acceptable evidence that chelation therapy with EDTA is effective for the treatment of atherosclerosis and the adverse effects of the drug can be lethal.' The American Heart Association has also reviewed the data and found no scientific evidence to support claims of benefit in patients with atherosclerosis. This opinion is shared by the American College of Physicians, the American Academy of Family Physicians, the American Society for Clinical Pharmacology and Therapeutics, the American College of Cardiology, and the American Osteopathic Association."[6]

It is obvious that strong opinions are held on both sides of this issue. Yet, is there a valid scientific basis for these opinions? To answer this, we performed computer literature searches using MEDLINE, the bibliographies of all articles and books identified, and obtained citations from the American Academy of Medical Preventics (Beverly Hills, CA). All identified sources citing original cases are included.

Supportive Evidence

The bulk of published experience with EDTA chelation therapy appears in the form of testimonials and poorly documented single case reports published in books and pamphlets by physicians using chelation in their practices.[4,5,7-18] One source states that in excess of 4600 documentary reports exist supporting chelation therapy.[12] In 1988, the American Academy for Advancement in Medicine compiled 3539 abstracts on EDTA chelation submitted by members.

By 1982, more than 1800 scientific journal articles had been published in English about various aspects of EDTA chelation.[13] However, we were able to locate no more than

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50 articles relating to atherosclerosis, few of which contained useful data. The articles reporting EDTA use in atherosclerosis are summarized in Table 1.[19-37] Fifteen articles are case reports including from 1 to 1974 patients who almost uniformly demonstrated "improvement." Commenting on this literature, Walker and Gordon observed that "EDTA chelation therapy has provided an overall average 82 percent success rate...."[13] One report warrants further comment because of the large number of patients.

Olszewer and Carter published their results from 1974 consecutive patients treated with open-label EDTA 50 mg/kg two to three times weekly for 20–40 treatments. Vitamins C and B and magnesium were added to the infusions. Patients modified their diets and physical activity. Measurements of endpoints (e.g., exercise tests, echocardiography, ventriculography, local temperature and trophic changes, Doppler ultrasound) were not uniformly applied and often were subjective and qualitative. EDTA chelation therapy resulted in "marked" improvement in 76.9 percent and "good" improvement in 16.6 percent of patients with ischemic heart disease and "marked" improvement in 91 percent and "good" improvement in 7.6 percent of patients with peripheral vascular disease.[29]

These case reports[19-37] are of limited scientific value in validating the efficacy of chelation therapy. All but three describe fewer than 100 patients, nearly all of whom were selected for study nonconsecutively, thus possibly introducing bias. The patients were treated for various diseases or the diseases were not specified. There were no controls. EDTA treatment regimens varied and some were potentially confounded by additional agents such as vitamins and dietary changes. Neither the patients nor investigators were blinded. Most reports used symptomatic improvement as the treatment outcome, which is an inherently biased measurement.

Two studies used a longitudinal design, that is, measurement of the variable of interest before and after treatment. Casdorph and Farr examined left ventricular resting ejection fraction by nuclear scintigraphic ventriculography before and after 20 infusions of open-label EDTA 3 g plus vitamin and mineral supplements in 18 patients, aged 48–72 years, with documented arteriosclerotic heart disease. All patients improved symptomatically, and 16 had complete subsidence of angina. Ejection fraction increased from 59.8 ± 9.9 to 65.6 ± 8.9 percent ($p<0.0005$).[33] Riordan et al. performed a uniform measurement of outcomes using the Cornell Medical Index Questionnaire before and after receiving a series of 20 open-label EDTA infusions for various health problems in 28 nonconsecutively chosen patients. In the questionnaire, patients were asked to respond by checking the "yes" option in response to a symptom description item if they experienced any of 195 symptoms. After 10 and 20 infusions, the group as a whole had fewer overall symptoms reported, with significant single-system improvement in cardiovascular, digestive, and nervous system symptoms ($p=0.01$).[28] These studies can be criticized for the small numbers of subjects and their open-label design.

Two clinical trials attempted to support chelation. In a double-blind study, Kitchell et al. administered EDTA to 4 patients and placebo to 5 patients with angina. Two patients receiving EDTA symptomatically improved compared to none who received placebo.[23] In 1989, Olszewer et al. attempted a randomized, placebo-controlled trial in 10 subjects with peripheral vascular disease but aborted the trial reportedly because of profound improvement in the patients receiving EDTA and those patients' subsequent refusal to accept placebo. Apparently, the blinding protocol was violated.[34]

Table 1. Published Results of Chelation Therapy

REF.	n	DISEASE	OUTCOME MEASUREMENT	RESULT
Case reports				
Clarke et al. (1956)[19]	20	CAD	symptoms	19 improved 1 died
Meltzer (1960)[20]	10	CAD	symptoms ECG	9 improved 5 improved
Clarke et al. (1960)[21]	76	CAD	symptoms	58 improved
	31	PVD	symptoms	27 improved
Kitchell et al. (1961)[22]	10	CAD	symptoms	9 improved
Kitchell et al. (1963)[23]	28	CAD	symptoms ECG exercise time	18 improved 13 less segment changes 1 died 18 increased
Lamar (1964)[24]	15	PVD	symptoms	15 improved
Lamar (1966)[25]	3	CAD	symptoms	1 improved 2 died
	1	PVD	symptoms	1 improved
AAMP (1981)[26]	18	CAD	symptoms	17 improved
Robinson (1982)[27]	248	unspecified	symptoms	not reported
Casdorph and Farr (1983)[33]	4	PVD	symptoms/signs	4 improved
Olszewer and Carter (1988)[29]	844 1130	CAD PVD	symptoms, ETT symptoms, signs ETT, Doppler	821 improved 1031 improved
McGillen and Mancini (1988)[35]	1	CAD	angiography	severe CAD
Godfrey (1990)[30]	27	PVD	Doppler	25 improved
Winebaugh et al. (1990)[36]	1	CAD	angiography	severe CAD
Deycher (1992)[31]	623	PVD	symptoms	70% improvement
	215	CAD	symptoms	70% improvement
Longitudinal studies				
Casdorph (1981)[32]	18	CAD	ejection fraction	17 improved
Riordan et al. (1989)[28]	28	unspecified	symptoms	18% fewer symptoms
Clinical trials				
Kitchell et al. (1963)[23]	9	CAD	symptoms	2/4 vs. 0/5 improved
Olszewer et al. (1989)[34]	10	PVD	symptoms	not reported
Guldager et al. (1992)[37]	153	PVD	symptoms ETT distance (m) Doppler index	36/75 vs. 39/78 improved 97 vs. 119 improved 0.56 vs. 0.53 improved

AAMP = American Academy of Medical Preventics; CAD = coronary artery disease; ECG = electrocardiogram; ETT = exercise-tolerance test; PVD = peripheral vascular disease.

Critical Evidence

Not all patients improve with EDTA chelation therapy. Five cases have been published reporting poor outcomes. Clarke et al. reported the sudden death of a patient with angina after receiving 15 treatments of intravenous EDTA 75 g.[19] Kitchell et al. reported that 1 of 28 patients had a fatal myocardial infarction after 51 infusions of EDTA in spite of markedly improving his Master's step test performance.[23] In two diabetic patients who died, Lamar noted severe generalized arteriosclerosis at autopsy in spite of previous EDTA therapy.[25] McGillen and Mancini published the results of quantitative coronary angiography on a 55-year-old man performed both before and after a 30-week treatment course of EDTA. Lesion cross-sectional area, percent of luminal diameter stenosis, and mean lesion length increased; mean minimal lumen diameter decreased after treatment. A 100 percent lesion in the right coronary artery remained unchanged after EDTA.[35] Winebaugh and Geraets described a 65-year-old man with stable angina who underwent a six-month course of 50 EDTA infusions. One month after the last infusion, he developed increasing chest pain occurring with minimal exertion. Coronary angiography revealed total occlusion of the right coronary artery. They speculated that that occlusion probably coincided with the exacerbation of angina.[36]

The only successful clinical trial was performed in Denmark by Guldager et al., who treated 153 patients (age 65 ± 9 y) with stable, intermittent claudication. Subjects were randomized to receive 20 infusions given over five to nine weeks of Na_2 EDTA 3 g or NaCl 8.4 g in 1000 mL of sterile water. Vitamin, trace element, and mineral supplements were added to the EDTA infusate. Pain-free treadmill walking distance, maximal walking distance, systemic ankle blood pressure index, and patient symptoms were assessed before and after the infusions. No treatment differences, including symptoms, were observed after three and six months of follow-up.[37] This trial is the only scientifically valid one published. It used random allocation of treatment, double-blinding, a parallel-placebo group, and measurable outcome variables. It can be argued that this trial may have insufficient statistical power and is one of the few negative reports to date (possibly because of publication bias). Nonetheless, a well-designed clinical trial must be given weight over the reports and small, poorly designed longitudinal and placebo-controlled studies. Parenthetically, two double-blind clinical trials initiated in US military hospitals have been aborted because of lack of funding.[30]

Adverse Effects

EDTA was first used in the treatment of lead intoxication, in doses ≥5 g/infusion. Both fatal and nonfatal renal toxicity were reported.[38,39] In rats, EDTA infusion caused dose-dependent, severe, hydropic degeneration of proximal renal tubules with casts and epithelial cells in the urine sediment.[38] The median effective dose in animals receiving 16 daily infusions was 203 mg/kg/d, equivalent to ≤3 g/infusion, which is the dose now used in clinical settings.[40,41] Three studies have measured renal function (serum creatinine, urea nitrogen) in 491 patients before and after prolonged courses of 3-g infusions of EDTA and have found no adverse changes.[42-44]

Table 2. Comparison of Adverse Effects of EDTA Infusion and Placebo[a]

ADVERSE EFFECT	EDTA	PLACEBO
Phlebitis at infusion site	35	28
Fatigue	12	11
Renal complications		
S-creatinine increase	7	9
proteinuria	10	4
Faintness	11	1
Gastrointestinal symptoms	11	1
Pain at infusion site	9	5
Headache	7	7
Hypocalcemic symptoms	6	2
Dermatitis	1	0
Metallic taste	1	0
Raynaud's phenomenon	1	0
Stroke	1	0

EDTA = ethylenediamine tetraacetic acid.
[a]Adapted with permission.[37]

The most frequent adverse effect of EDTA is a burning sensation at the infusion site, which diminishes with lower infusion rates (≤750 mg/125 mL/h).[45,46] Other, much-less-frequent effects include thrombophlebitis (probably related to concentration of the solution); hypotension; hypocalcemia, occasionally with tetany (after rapid administration); malaise, fever, myalgia, and headache in a characteristic sequence often heralding renal toxicity; nausea, vomiting, and diarrhea; glycosuria; insulin shock; histamine-like reactions; anemia; exfoliative dermatitis (probably due to vitamin B_6 depletion); systemic emboli; bone marrow depression; prolonged prothrombin time; pseudothrombocytopenia; and cardiac arrhythmias.[1,36,45-49]

To minimize the adverse effects, the American College of Advancement in Medicine recommends the following protocol:[46]

1. EDTA 50 mg/kg (maximum 5 g) diluted in 500–1000 mL of an 150-osmolar carrier;
2. add heparin 1000–2000 units, sodium ascorbate 4–20 g, elemental magnesium 200 mg, lidocaine 2% 1–10 mL, pyridoxine (B_6) 50–300 mEq, and sodium bicarbonate 10 mEq;
3. optional additives include adrenal cortex extract, cyanocobalamin (B_{12}), niacin, pantothenic acid, and vitamin-B complex;
4. infuse over four hours.

Guldager et al. used an EDTA infusion protocol similar to the one above in a randomized, double-blind, placebo-controlled trial in which 153 patients received 20 infusions. As shown in Table 2, the adverse effects experienced by the EDTA treatment group were not significantly different from those in the placebo group.[37] EDTA infusions as outlined above probably are safe.

Pharmacology

EDTA was synthesized in 1930 and patented in 1949. It is a complex molecule whose only recognized pharmacologic action is the chelation of divalent and trivalent ions such as calcium, zinc, cadmium, manganese, lead, vanadium, and plutonium.[50-52] Following oral administration, 80–95 percent of the dose appears in the feces within 24 hours. After intravenous administration, 95 percent of the

dose appears in the urine within 24 hours. Less than 0.5 percent remains in the body after 48 hours (half-life one hour). EDTA is not metabolized. Renal clearance is similar to that of inulin and is not affected by alterations in urine flow rate or pH, although impaired renal function delays excretion.[53]

The chemical binding of various cations to EDTA has a distinct order of preference, listed from most to less avidly chelated: Cr^{2+}, Fe^{3+}, Hg^{2+}, Cu^{2+}, Al^{3+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Ca^{2+}, and Mg^{2+}.[46] Parenteral EDTA rapidly binds serum calcium and can produce tetany with rapid administration.[47] Slower rates of administration do not affect serum calcium concentrations, but mobilize bone calcium and induce hypercalcicuria (Ca^{2+} >600 mg/24 h urine volume).[46]

Possible Mechanisms of Action

Recent advances in the understanding of the pathogenesis of atherosclerosis have resulted in the postulation of several biologically plausible mechanisms of action for EDTA chelation. It is now believed that oxidative modification of low-density-lipoprotein cholesterol (ox-LDL-C) is a crucial step in the process whereby subendothelial macrophages and arterial myocytes avidly take up ox-LDL-C, which, in turn, stimulates secretion of numerous chemotactic agents and cytokines.[53,54] Phenotypically modified arterial myocytes migrate to the subendothelial space where they secrete fibrin, collagen, and proteoglycans which form the mature fibrous atherosclerotic plaque.[55,56] Divalent and trivalent cations appear to serve as catalysts and cofactors in these processes.[56-59] The following are several possible mechanisms for EDTA's action against atherosclerosis.[60]

The authors of the first article on EDTA therapy for atherosclerosis believed that its effect was due to decalcification of the atherosclerotic plaque.[14] In human cadaveric iliac arteries, EDTA mobilized 30-fold more calcium from atherosclerotic plaque than did NaCl 0.9%.[61] EDTA has reversed plaque formation in vivo in atherosclerotic rabbits.[62] With increased urinary excretion of calcium, there is parathormone-induced recruitment of calcium from labile stores, some of which is metastatic pathologic calcium.[63,64]

EDTA may inhibit free-radical oxidization of LDL-C and other moieties by depletion of the metal ions necessary to catalyze the Fenton reaction,[58] which is absolutely dependent on low concentrations of copper or iron and is therefore completely inhibited in vitro by EDTA or other metal chelators.[53] In humans, a direct relationship has been demonstrated between the concentration of copper and severity of atherosclerosis.[65,66] The exact role of iron in metalloenzyme-induced oxidation remains to be elucidated, but iron at least is involved as a cofactor to the enzyme catalase.[67] Although high stored iron concentrations appeared to induce atherosclerosis in one study,[59] another found no effect.[68]

By decreasing calcium in the subendothelial space and within myocytes, EDTA might inhibit vasoreactivity, myocyte migration, and lipid metabolism. Such effects have been demonstrated by calcium-channel blocking drugs.[57,69-71] Clinical trials have shown retardation of angiographic progression of atherosclerosis in subjects treated with calcium-channel blockers.[72,73] Parenthetically, magnesium depletion (which may be induced by EDTA) appears to accelerate atherosclerosis.[74,75]

Gordon and Vance list several other, less-appealing possible mechanisms, including inhibition of phosphodiesterase with increased glycogenolysis, clearing of intracellular heavy metals, alteration of tryptophan metabolism, improved lipid metabolism, alteration of red blood cell membranes resulting in increased deformability, lower blood pressure due to calcium and zinc excretion, and changes in connective tissue induced by parathormone.

Summary

Although much has been written about EDTA chelation therapy for atherosclerosis, very little scientific evidence has been offered. Through this morass of differing opinions, it must be agreed that any therapy applied to patients must be both safe and effective. EDTA does appear to be safe when used in doses ≤3 g per infusion. This is based both on the large numbers of patients treated without reported adverse effects and the safety data from the only large clinical trial.[37] Because of the poor scientific quality of the supporting reports, one must conclude that EDTA's efficacy is unproven. Indeed, the best evidence available favors lack of efficacy.[37] Therefore, EDTA chelation therapy cannot be recommended for clinical use.

Nonetheless, EDTA chelation therapy should not be totally rejected. The postulates that EDTA might favorably alter metalloenzyme-induced oxidation and calcium-mediated processes in atherogenesis are enticing. Animal studies seem warranted. ≃

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EXTRACTO

OBJETIVO: Determinar la eficacia y seguridad del agente quelante, ácido etilenodiaminatetracético, en el tratamiento de la aterosclerosis.

FUENTES DE INFORMACION: La literatura evaluada se identificó utilizando el sistema MEDLINE (1966 a Mayo del 1993) y a partir de la bibliografía de los libros y artículos así identificados. Se obtuvo información adicional de la American Academy of Medical Preventics. Se evaluaron 16 reportes descriptivos, dos estudios longitudinales, tres estudios clínicos, y casos adicionales descritos en 19 libros.

SINTESIS DE INFORMATION: Existe poca evidencia científica válida para apoyar el uso del EDTA en el tratamiento de la aterosclerosis. Aunque los mecanismos de acción postulados son biológicamente posibles, y el uso de EDTA en dosis menos de 3 g/infusión parece ser seguro, no se ha demostrado la eficacia de este tratamiento. De hecho, la mejor evidencia demuestra que esta terapia es ineficáz. Por lo tanto, no se recommienda usar la quelación con EDTA en el tratamiento de la aterosclerosis.

CHRISTINA DALMADY-ISRAEL

RESUME

OBJECTIF: L'objectif de cet article est de déterminer l'efficacité et la sécurité de l'acide tétra-acétique d'éthylènediamine (EDTA) en tant qu'agent chélateur dans le traitement de l'athérosclérose.

METHODOLOGIE: Les références ont été identifiées à partir d'une recherche informatisée couvrant la période de 1966 à mai 1993.

RESULTATS: Seize rapports de cas ou séries de cas, deux études longitudinales, trois études cliniques, ainsi que des citations de livres ont été revisées.

CONCLUSIONS: Bien que son mécanisme d'action proposé soit rationnel et que il soit bien toléré, il n'existe pas d'évidence scientifique concernant l'efficacité de l'EDTA dans le traitement de l'athérosclérose. Ainsi, cette thérapie devrait être évitée.

MARC PERREAULT

EDTA CHELATION THERAPY FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEA

The Medical Letter continues to receive inquiries about the value of edetate disodium (EDTA) chelation therapy for cardiovascular disease. The last Medical Letter article on this subject was published in 1981 (volume 23, page 51). Some authors have estimated that more than 500,000 people receive this form of treatment each year (MT Grier and DG Meyers, Ann Pharmacother, 27:1504, Dec 1993).

RATIONALE — EDTA chelates divalent and trivalent ions such as calcium, zinc, lead, iron and copper, which are then excreted in the urine. Proposed mechanisms of action for EDTA treatment of atherosclerosis include removal of calcium from atherosclerotic plaques and depletion of iron and copper necessary for enzyme-induced oxidation of lipoproteins (S Parthasarathy and D Steinberg, Curr Opin Lipidol, 3:313, 1992).

CLINICAL TRIALS — Most published reports supporting EDTA chelation therapy for atherosclerosis are in the form of testimonials and case reports (EM Cranton and A Brecher, *Bypassing Bypass: The New Technique of Chelation Therapy*, New York:Stein and Day, 1990). The only large case-series included 1974 consecutive patients treated in a chelation clinic with open-label EDTA 50 mg/kg two to three times weekly for 20 to 40 treatments. Non-blinded and non-uniformly applied outcome measurements noted "improvement" in 93.5% of patients with ischemic heart disease and in 98.6% of those with peripheral vascular disease (E Olszewer and JP Carter, Med Hypothesis, 27:91, 1988). An uncontrolled longitudinal study of 18 patients before and after 20 infusions of open-label EDTA, 3 grams per infusion, found symptomatic improvement in all patients and an average increase of 5.8% in ejection fraction (HR Casdorph, J Advancement Med, 2:121, 1989). In the only well-designed clinical trial published on this subject, 153 patients with severe intermittent claudication were randomized to receive 20 infusions of EDTA, 3 grams per infusion, or saline over five to nine weeks; no statistically significant differences in pain-free or maximum walking distances were observed between EDTA and placebo after the 20 infusions or three and six months later (B Guldager et al, J Intern Med, 231:261, 1992).

ADVERSE EFFECTS — Renal toxicity (sometimes fatal), cardiac arrhythmias, bone marrow depression, exfoliative dermatitis, histamine-like reactions, insulin shock, and thromboemboli have occurred with use of chelation therapy, but few adverse effects have been reported when a protocol using 50 mg/kg per infusion of EDTA was followed as recommended by the American College of Advancement in Medicine (EM Cranton, *A Texbook on EDTA Chelation Therapy*, New York:Human Sciences Press, 1989, page 269). A double-blind study using a similar protocol found no apparent increase in adverse effects compared to placebo in 56 patients followed for six months (B Guldager et al, cited above).

CONCLUSION —There is no acceptable evidence that EDTA chelation therapy is effective for treatment of cardiovascular disease.

Correction — Cost of Delivery System for Aerosolized DNase: In the April 15 article on DNase *(Pulmozyme)*, the third sentence in the "Dosage and Cost" paragraph on page 35 should be: "The delivery system costs about $200 for a compressor and $17 for a reusable nebulizer."

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CMAJ, Vol 140(7): 829-831, 1989

Health Care

Chelation therapy and Uncle John

Robert Patterson, MD

My Uncle John telephoned the other day to discuss some health concerns. Nothing unusual about that. As the only MD in the extended family, relatives occasionally solicit my "expert medical opinion", especially now that I'm in my internship year. I already knew from past conversations with my uncle that he had been recently diagnosed as having mitral valve prolapse and coronary artery disease, for which bypass surgery had been recommended.

"What do you know about using EDTA for atherosclerosis?" Uncle John asked. Educated at UCLA and an executive in the energy business until his retirement a few years ago, he is the sort of person to read avidly about his health. My answer was straightforward. I had never heard of it.

"Do you know it's an alternative to bypass surgery?"

No I didn't.

"Did you know that over 400 000 people in the US have been treated with EDTA?"

No I didn't.

"Did you know that people who suffered terribly from angina and a multitude of other diseases have been completely cured by EDTA?"

No I didn't.

By this time I wondered how I had missed hearing about such an important drug. Were there deficiencies in my medical school curriculum? Or had I skipped that lecture to go skiing? Thank goodness there were no LMCC questions about EDTA.

"I'm going to send you a copy of a book I've read. I want you to evaluate it and let me know what you think." With that, Uncle John bade farewell.

Needless to say, my curiosity was aroused. After I put down the phone I picked up *Harrison's Principles of Internal Medicine* and brushed off the dust that had accumulated since the start of my internship. EDTA was indeed listed in the index and there was a paragraph promoting its use as a chelating agent in heavy metal poisoning. Nothing about atherosclerosis, though. Hmm. How could this prestigious textbook not have included such a significant therapeutic agent?

The next day at the hospital I asked several of the other interns, including two aspiring cardiologists, what they knew about EDTA. No one had heard of it. One of the cardiovascular surgeons just laughed.

A few days later a brown paper package arrived in the mail. I eagerly tore it open and began to read. *Bypassing Bypass*[1] was published in 1984 and devoted entirely to chelation therapy. One of the authors was a graduate of Harvard medical school, a diplomate of the American Board of Family Practice, and a past president of the American Holistic Medical Association.

The book began with a brief history of chelation therapy, from its infancy in the 1940s, when it was used to deal with arsenic and metal poisonings, through to its present-day use for atherosclerosis. Several heartwarming vignettes were recounted about patients who suffered from severe coronary artery disease or gangrenous limbs and courageously ignored their doctors' recommendations of surgery, opting instead for chelation therapy and thereby experiencing cures that were nothing short of miraculous.

What exactly is chelation therapy? The authors define it as "a medical treatment that improves metabolic and circulatory function by removing toxic metals (such as lead and cadmium) and abnormally located nutritional metallic ions (such as copper and iron) from the body. This is accomplished by administering a synthetic amino acid, ethylenediamine-tetra-acetic acid (EDTA), by an intravenous infusion . . ." (page 14).

This occurs, we learn, through the "free radical theory of disease": The pathogenesis of many disease processes has as a common denominator excess free radical production in the body, and through mechanisms not yet fully understood, the authors state, EDTA is believed to interfere with free radical formation. It may have other actions as well, stopping the advance of or even reversing the damage done to the body by several diseases. Chief among these diseases is atherosclerosis.

Scattered throughout the book are grandiose claims of other benefits reported anecdotally after EDTA therapy, so many in fact that I had to make a list to keep track of them all: reversal of atherosclerosis, as manifested by decreased symptoms of angina, reversal of gangrene, improved skin colour, warming of cold extremities and healing of chronic diabetic ulcers; decrease in symptoms of arthritis, multiple sclerosis, Parkinson's disease and psoriasis; reversal of Alzheimer's disease; improved vision, hearing

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and sense of smell; improved muscle coordination; decreased insulin requirement in diabetics; and decreased incidence of recurrent thrombophlebitis. The complete list is much longer — it includes increased sexual potency and libido — but these examples provide an idea of EDTA's alleged powers.

What a panacea! No wonder Uncle John considered delaying his bypass surgery in favour of chelation. Of course, the authors are quick to emphasize that not every patient experiences all of the aforementioned results, and they do not advocate the use of EDTA as a treatment for any disease other than atherosclerosis and other circulation-related problems.

Although it doesn't work for everyone, the authors claim that as of 1984 more than 400 000 people had received chelation therapy, and in his own private practice one of the authors has experienced "marked and lasting benefit in 75 to 95 per cent of hundreds of patients treated" (page 106).

Not too surprisingly, the authors have many criticisms of coronary artery bypass grafting, citing its skyrocketing cost and high morbidity and mortality and arguing that it is used too soon and too often, instead of being saved as a last resort after all other modalities of treatment have been found wanting.

How does a patient obtain chelation therapy, and what exactly is it? A patient must first find a chelation physician, preferably one approved by the American College of Advancement in Medicine, a professional body of physicians that offers a sort of "board certification" in chelation therapy. Before commencing any treatment, the patient undergoes a complete history and physical, as well as a battery of laboratory tests that includes chest radiography, electrocardiography, stress test, biochemical profile, 24-hour urinalysis and analysis of a snip of hair in order to "screen your nutritional mineral and trace element status and determine whether your body has accumulated excessive toxic metals" (page 126).

The treatment itself consists of an IV infusion that usually contains 3 g of EDTA, plus a vitamin and mineral cocktail, mixed in 500 ml of solution and dripped in slowly over 3 hours to avoid EDTA's nephrotoxic potential. Exact protocols may vary, but in most cases patients receive treatment two or three times per week for several months, then a follow-up treatment every 2 weeks for a variable period. Urine and blood samples are obtained prior to each infusion in order to monitor kidney function. A full course of treatment may consist of anywhere from 30 to 100 infusions, depending on the individual and the severity of the disease. Cost is $100 to $150 (US) per session, and in most cases it is not covered by medical insurance plans. (In our pharmacy, the cost of 3 g of EDTA is $12.)

In addition to the EDTA infusion, patients are asked to change their lifestyle in order to optimize treatment. Most chelating physicians have an interest in holistic medicine and promote these beliefs — patients are expected to quit smoking, limit their alcohol intake, exercise regularly, reduce their stress levels, take vitamin and mineral supplements and follow a health-promoting diet. In particular, one of the authors recommends his own "Anti-Free Radical Diet". Between the EDTA therapy and lifestyle changes chelation doctors report remarkable successes, and offer numerous patient testimonials as evidence.

So why hadn't I heard of chelation therapy before? Even if only a fraction of the claims are valid, EDTA would be worth prescribing. Determined to explore the literature, I asked our user-friendly librarian to run a Medline search. The results weren't too impressive — only a dozen listings from the last decade or so. What they reported, however, contrasted sharply with the authors' claims.

"Some profess that a certain intravenously administered colorless compound is the elixir of youth. Chelation therapy with edetate disodium (EDTA) solution is described in tones of evangelical fervor..." begins one paper. "There are several sites in the United States and Canada where this therapeutic fad currently is in vogue and where the zealot peddles these wares to the naive afflicted. Symposia and miniconventions have been organized to extol its virtues." [2]

An editorial states: "One of the most dangerous medical-social phenomena in recent years has been the appearance of 'chelation clinics' for treatment of cardiac and peripheral disease .... Such therapy is of no proven benefit in the treatment of atherosclerosis. Not only is efficacy unproven but there is great potential danger to such treatment .... Chelation therapy for atherosclerosis does not meet the standards of acceptable medical care for any community in the United States or any other country in the world."[3]

Strong words. Most other papers echo the same sentiments.[4-14] Sources of disparagement include the *Journal of the American Medical Association*, the *New England Journal of Medicine*, *Chest*, the *Medical Letter of Drugs and Therapeutics* and the *Harvard Medical School Health Letter*. One repeated objection is that the effectiveness of EDTA "has not been established in any well-designed controlled trial. Although some uncontrolled studies claim benefits, others have shown no substantial effects from such therapy".[4]

A second common concern is toxicity. "Severe adverse effects have been reported with EDTA administration including hypocalcemia, tetany, convulsions, cardiac arrhythmias, and respiratory arrest. Edetate disodium has caused acute tubular necrosis and death due to renal failure."[5]

Poor chelation therapy. It appears that no one in medicine's mainstream has anything nice to say on your behalf. One writer concludes with this lament: "How often we are baffled by patients whose symptoms of an-

gina pectoris or intermittent claudications are nonresponsive to treatment. No wonder that many laymen cherish the hope that the ultimate potion has been discovered. However, there can be only one response when a physician or patient asks, 'Do you know something we don't about this new "wonder drug"?' The sole response to this enquiry must be that we cannot recommend chelation therapy for the treatment of atherosclerosis because there are *no* data from controlled trials that demonstrate its efficacy."[2]

To their credit, the authors of *Bypassing Bypass* are aware of these and other criticisms and offer counterarguments. They claim that the nephrotoxic effects of EDTA can be avoided by slow administration of the drug and careful monitoring of kidney function. They also insist that there are numerous studies supporting the efficacy of chelation therapy, but many of these are published in foreign language publications or in journals not listed in *Index Medicus*, such as the *Journal of Holistic Medicine* and the *Journal of Orthomolecular Psychiatry*.[15-23]

As well, the authors feel strongly that a conspiracy exists among medical professionals to suppress inexpensive chelation therapy and promote the high-tech, glamorous — and costly — bypass surgery. Along a different financial line, they accuse pharmaceutical companies of refusing to underwrite the costs of investigating a product for which the patent has expired and that would, therefore, not be profitable. The authors are optimistic that in time the stiff-necked medical profession will be won over.

My conclusions after reading all of this? I like to think of myself as open-minded but sceptical. The anecdotes and documented recoveries of people who have been chelated are too numerous and too dramatic to shrug off entirely. On the other hand, some of the stories have a "too-good-to-be-true" flavour, and many steps are missing in understanding the mechanisms of how (or if) EDTA works.

According to an update at the end of the book, the American Food and Drug Administration issued an investigational drug number for EDTA in 1987, and since then several double-blind studies have been undertaken. I will reserve any further opinion until all the results are in.

In keeping with my uncle's request, I penned him a letter with my impressions and a caution that I would not, from what I know at present, recommend that he pursue chelation therapy in lieu of his bypass surgery. Before my letter arrived, Uncle John left home and drove down to the States to visit a chelating physician. He underwent a series of tests and was told he was suffering from chronic heavy-metal poisoning due to the fillings in his teeth. While watching an educational video on chelation therapy in the waiting room, my uncle experienced a sudden onset of crushing retrosternal chest pain with radiation down the left arm, accompanied by shortness of breath and nausea. He was rushed by ambulance to a local hospital, where emergency angioplasty cleared an occluded right coronary artery.

I spoke by phone to my uncle as he lay in his coronary care bed. He agreed rather sheepishly that he had explored the question of chelation long enough and would proceed with his bypass operation as soon as he was fit for surgery.

"But this heavy-metal poisoning from the fillings in the teeth, I found that really interesting", he added. "I'm going to send you some literature on it. Let me know what you think."

The author wishes to thank Cliff Cornish for his help in researching this article and wishes his Uncle John a speedy recovery.

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FROM: Ilisa B.G. Bernstein, Pharm.D., J.D.

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COMMENTS:

As requested - brief info regarding dietary supplement activities & legislation.

Ilisa

827-0589

Number of Pages, Excluding Cover 2

The "Dietary Supplement Health and Education Act of 1994" (DSHEA) (Pub.L. 103-417) was signed into law by the President on October 25,1994. DSHEA amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to alter significantly the way the Food and Drug Administration regulates dietary supplements and requires the Agency to undertake significant rulemaking and other actions to fully implement the scope of the Act.

In summary, DSHEA:

- redefines "dietary supplement" to include the following dietary ingredients: 1) a vitamin; 2) a mineral; 3) an herb or other botanical; 4) an amino acid; 5) another dietary substance for use by man to supplement the diet by increasing the total dietary intake; or 6) a concentrate, metabolite, constituent, extract, or combination of these ingredients. "Dietary supplements" will include articles previously approved as a drug, antibiotic, or biologic, or authorized for investigation, if they had been marketed prior to such approval or authorization as a dietary supplement, unless the Secretary issues regulations finding the article to be unsafe under the Act;

- places the burden of proof on FDA to prove that a product is unsafe before it can be removed from the marketplace;

- exempts certain third party literature from treatment as labeling if certain conditions are met with regard to content and presentation of the literature;

- establishes a series of labeling requirements with which manufactures must comply by December 31, 1996;

- allows dietary supplement manufactures to make statements of nutritional support ("structure" or "function" claims), under certain conditions without preclearance and without subjecting product to regulation as a drug. Statements claiming to diagnose, treat, cure, or prevent disease continue to subject product to regulation as a drug;

- provides authority for the Agency to develop and enforce good manufacturing practices for the dietary supplement industry;

- establishes a Commission on Dietary Supplement Labels to develop recommendations on labeling claims for dietary supplements and requires the Secretary to publish through notice and comment rulemaking the Commission's recommendations. If such rulemaking is not completed within 2 years of the issuance of the report, the NLEA final; regulations for health claims for dietary supplements, published January 4, 1994, will be null and void;

- creates an Office of Dietary Supplements within NIH to explore and study the role of dietary supplements in improving health and health care.

Most of the sections of DSHEA are self-implementing and do not require FDA to issue regulations. For some sections, however, the agency must issue regulations pursuant to the legislation or for conforming purposes with other legislative mandates (e.g., to conform with the labeling requirements for the Nutrition Labeling and Education Act of 1990).