The Correlation Between EDTA Chelation Therapy and Improvement in Cardiovascular Function: A Meta-Analysis

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ABSTRACT: In order to establish whether there is value in treating cardiovascular disease with intravenous EDTA chelation therapy, a meta-analysis was done, based on currently available scientific literature. A thorough literature search identified 40 articles on the subject. Nineteen studies met the criteria for inclusion with data on 22,765 patients. The meta-analysis revealed a correlation coefficient of 0.88, which indicates a high positive relationship between EDTA therapy and improved cardiovascular function. Eighty-seven per cent of the patients included in the meta-analysis demonstrated clinical improvement by objective testing.

Introduction

A minority of physicians throughout the world use EDTA chelation therapy to treat atherosclerotic cardiovascular disease. More conventional physicians have from time to time expressed editorial criticism of this treatment, usually claiming that there is little evidence that it is effective(1-5). Chelating physicians insist that their clinical results are excellent and that attempts to publish their data have been rejected by more widely read and indexed journals(6,7).

Recently, meta-analysis has emerged as a technique to examine controversial issues in medicine. Experts have proclaimed that it is an effective tool for comparing studies evaluating drugs or medical

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procedures. Examples include Lau's(8) meta-analysis of therapeutic trials for myocardial infarction and Muldoon's(9) dramatic finding that reduced cholesterol concentrations do not affect overall survival, based on a meta-analysis.

The authors decided to use a meta-analysis to determine the likelihood that EDTA chelation therapy has a positive effect on cardiovascular disease, based on currently available literature.

Techniques for Literature Search

A Medline search revealed that there have been only a few articles published in prominent medical journals. Exerpta Medica, Current Contents, and the French PASCAL databases produced considerably more material. A Science Citation Index search for ten key authors was also performed. Health Periodicals Database and Toxline were scanned. The American College of Advancement in Medicine provided a collection of 80 key articles on the therapeutic use of EDTA(10). It also offered a substantial volume of abstracts(11) from the world literature on many aspects of the use of chelation therapy. The Journal of Advancement in Medicine has been published since 1987 and has included several important articles on the subject. Since this journal has not been included in the above data bases, individual issues of it were obtained and searched. Finally, individual authors and clinicians were contacted, both to examine their files for additional studies and to provide the raw data from their published studies if it had not been presented in a form needed for the meta-analysis.

Selection of Studies

Criteria were established as follows for the inclusion of studies in the meta-analysis:

1. Limited to human studies;
2. Include only data that specified whether or not the subjects improved;
3. Include only data that referred to objective measurement of improvement in cardiovascular disease.

Because of the strictness of the criteria chosen, many studies were omitted from the meta-analysis. Since the great majority of those

omitted showed positive results, it is estimated that inclusion of them would not have significantly changed the outcome of the meta-analysis. However, confidence in the outcome might have been even stronger because of the larger number of studies and subjects considered in the analysis. Numerous animal studies(11,12) show positive effects of EDTA and shed light upon the mechanism of action, but were not included.

A number of important human studies were omitted because they limited their observations to the net statistical change in a group of patients. Although data reported in this form contains much useful information, the studies did not conform to the required criteria. McDonagh, Rudolph and Cheraskin(13) published a collection of 27 articles on the efficacy of EDTA chelation therapy that were originally published in various journals. All but four of them fit this category. One(14) that was included in the meta-analysis because it listed data on individual patients described 30 patients whose carotid artery obstructions were reduced by almost 50 per cent. Riordan and Cheraskin(15,16) published one study on EKG changes and another using the Cornell Medical Index to document clinical change. Guldager and associates(17) in Denmark, a group of cardiovascular surgeons, authored a controversial study in this category that will be discussed in more detail below. The above authors were contacted in an attempt to obtain the raw data on individual patients so that material could be extracted for inclusion in the meta-analysis. Unfortunately, none of the extractions became available in time to be included. Since all these studies were strongly positive except Guldager's, the authors do not feel that they would have impacted the results significantly.

Other reports that contained insufficient data include Robinson's (18) review of 248 patients with various cardiovascular diseases. He commented that the vast majority had symptomatic improvement. Magee(19) mentioned one case treated with EDTA that subsequently required aorto-femoral surgery, but no pre and post testing was offered. Wirebaugh(20) contributed a case report of a patient who improved symptomatically with EDTA but later underwent angioplasty for single vessel disease. The patient did not suffer an infarction, and the only before and after testing listed were negative exercise treadmill tests 5 months after chelation and again after angioplasty. The first case of reversal by chelation therapy of cardiomyopathy due to iron overload was described by Rahko, Salerni, and Uretsky(21). Deferoxamine instead of EDTA was used as the chelating agent, but both substances remove iron effectively(22).

Several early papers, especially those by Lamar(23,24), Clarke and associates(25-28) and Evers(29), were highly influential because they stimulated many physicians to begin to offer chelation therapy to their patients. These works were omitted because they consisted of large collections of case studies which did not specify objective testing that confirmed that subjects improved with therapy. Olwin and associates(30) and Langhof and associates(31) made general observations, particularly about plasma lipids.

Articles or parts of articles that referred to other chronic degenerative diseases such as scleroderma, Parkinson's disease, osteoporosis, chronic obstructive pulmonary disease, cancer, porphyria and Alzheimer's disease were omitted. More difficult to assess were several articles each on digitalis-induced arrhythmias(32) and reduced left ventricular ejection fraction in Thalassemia Major(33), both of which were treated successfully with EDTA chelation. These were not included because there were extraneous causes for the cardiovascular problems. A summary of the articles that pertained to EDTA chelation therapy and cardiovascular disease, but were not included in the meta-analysis, is contained in Table 1.

The authors were able to find references to six double or single blind studies with controls. All present certain problems. The most reliable appears to be the single-blind cross-over study of 10 patients by Olszewer and Carter(34). Because the differences between the EDTA treated patients and those who received placebos were so dramatic, the code was broken early and both groups were treated with EDTA. This was ethically the correct step to take, but the study has somewhat less statistical significance because of the atypical design.

Sloth-Nielsen and associates(35) and Guldager and associates(17) published two papers in separate journals on the same clinical trial showing no significant improvement in peripheral vascular patients treated with EDTA. The first paper selected 30 patients who were given angiograms and transcutaneous oxygen tension measurements before, during and after treatment. Twenty-nine of the patients were smokers. The second paper reported on the mean walking distance of all 153 patients, half of which were given a placebo. Seventy percent of the subjects were smokers and continued to smoke. Three critiques of these papers(36-38) have been published, based on interviews of patients and nurses who participated in the study. It is contended by Cranton and Frackelton that smokers were deliberately chosen to be subjects and patients were instructed to take iron-containing tablets during the treatment period, both of which would tend to lessen the

TABLE 1

Studies Linking EDTA with Cardiovascular Disease Not Used in Meta-Analysis

Author	Journal & Date	Diagnosis	Test	No. of Subjects	Results
McDonagh, et al	Med Hyp/81	Hyperlipidemia	Cholesterol	221	Chol reduced ave of 25-31 points
McDonagh, et al	Med Hyp/82	Hyperlipidemia	Chol/HDL Ratio	358	Low ratios rise, high ratios fall
McDonagh, et al	J Ortho Psy/82	CAD/Fatigue	Cornell MedIndex	95	Fatigue scores imprvd by 39%
Cheraskin, et al	Jofl AP Med/84	CAD	HR w/ SEKG	50	HR decreased by 8.7 to 9.2%
McDonagh, et al	J Ortho Psy/85	Pts w/Chronic Dis	Cornell MedIndex	139	Symptoms scores red. by 13-31%
Riordan, et al.	J Ortho Med/89	Hypertension	Cornell MedIndex	28	23% symptom reduction
Riordan, et al	J Adv Med/88	Elev Lead Levels	QRS Interval	28	Reduced interval .07 to .064
Lamar	J Am Ger Soc/66	CAD, PVD, CVD	Non-Inv Vasc Test/Symptoms	53	Marked imprvmnt, dementia and vision better
Lamar	Angiology/64	PVD, CAD, DM	Symptoms Decr Insulin	15	All improved, insulin red. in 7
Boyle, Clarke	Fed Proc/61	CAD, Angina	Symptoms/EKG	10	9 Improved, sev had better EKG's
Clarke, et al	A J Med Sci/55	Angina, PVD	Symptoms	22	Unusual symptoms relief/ hearing imp
Clarke, et al	A J Med Sci/60	CAD	Symptoms	76	96% improved
Clarke, et al		Interm Claudic	Symptoms	31	87% improved
Clarke, et al		CVD	Symptoms	25	100% improved
Clarke	A M J Card/60	PVD, CAD, CVD	Symptoms	Sev Hundred	>87% improved incr. WD, decr Mort

TABLE 1 (*Continued*)

Author	Journal & Date	Diagnosis	Test	No. of Subjects	Results
Robinson	N Z Med J/82	CAD, PVD, HBP	EKG/BP, Pain	248	Pain relieved, BP & EKG's better
Evers	ACAM/79	CAD, CVD, PVD	Symptoms w/dist	3,000	> 90% Improved
Olwin, et al	Soc Exp Biol/68	Hyperlipidemia	Plasma Lipids	34	Lipids lowered, esp. trigl.
Langhof	Proc Angiol/61	PVD, High Chol	Symptoms/Chol	12	Sympt. improved, Chol lowered
Hancke, et al	–/93	CAD	Working Capac	208	84% Improved
Hancke, et al			Angina Sympt	162	91% Improved
Hancke, et al			NTG Demand	133	92% Improved
Guldager, et al	J Int Med/92	Severe PVD	WD, A/B Index	66	EDTA pts imprv more than placebo group, but diff not statistically significant
Magee	Med J Aust/85	PVD	Need for Surg	1	Failed treatment
Wirebaugh, et al	DICP An Ph/90	CAD	Need for Angiopl	1	Failed treatment
Rahko, et al	J A Coll Card/86	cardiomyop	Symptoms	1	Recovered - DFO, not EDTA
Diehm	Z Deut Herz/86	PVD	W Dist	24	Both EDTA & Bncy impr 70-76% EDTA was better at 3 mos. Not statistically significant

benefits of EDTA considerably. They also state that the study was not blind as claimed, that pain at the IV site was not as expected and that some patients who claimed to be better were placed in the category of no improvement. Although these allegations are disturbing, judgement is not made on them at this time. Further observations reveal that the study involved very sick patients with A/B indices averaging 0.5, limited treatment (20 IV's), and the omission of intravenous magnesium from the standard protocol. Patients receiving EDTA improved more than placebo treated patients in both walking distance and A/B index at 6 months followup, but the results were not statistically significant. According to the criteria, the first paper is included in the meta-analysis because it reports results for individual patients. The second is omitted because the data needed on the individual patients for this study were not available.

Olszewer and Carter refer to a double-blind study done at the University of Heidleberg in Germany by Diehm(39). The study compared intravenous EDTA to benzcyclan (a vasoactive drug that is also an anticoagulant) in the treatment of peripheral vascular disease for 45 patients. Both groups improved by 70-76% in walking distance, although three months after treatment, the EDTA group reported a greater improvement. The author concluded that the improvement was a "placebo effect", even though no placebo was used. Olszewer and Carter(40) stated that the raw data revealed that four patients treated with EDTA experienced more than a 1000 meter increase in walking distance but were excluded from the statistical analysis as outliers. It was also shown that 7 out of 10 patients with gangrene made satisfactory recoveries with EDTA chelation therapy. Since the paper itself did not reveal data on individual patients, it was not included in this meta-analysis.

A double-blind study of a small sample of patients was apparently completed at Baylor University School of Medicine several years ago, but the results have not yet been published, and the raw data were not obtainable. Foundation Partners, Inc. is the holder of an Investigational New Drug permit issued by the Food and Drug Administration and is cosponsor of a FDA approved, double-blind study of EDTA treatment of vascular disease. Martin Rubin and Ross Gordon were instrumental in designing and working out the specifics of this study, which has not yet been completed. Another ongoing study by Van Rij in New Zealand is nearing completion. None of these studies were available for the meta-analysis.

Hoekstra, Gedye, Scarchilli, Parente and associates(41) have com-

pleted a large retrospective study of 19,147 patients utilizing thermography pre and post EDTA treatment for peripheral vascular disease. In spite of its being unpublished, the so-called "Cypher Study" has been allowed as evidence in several legal proceedings and was instrumental in obtaining government acceptance of the treatment in New Zealand. The authors allowed use of the pre-publication draft of their paper for this meta-analysis. All patients had at least moderate stenosis and 86% of them showed measurable improvement after treatment with EDTA. A control group of 64 patients did not improve. The statistician conducted a blinded reanalysis of the data for a representative sample, which confirmed the results.

There is no question that the Kitchell and Meltzer study(42) should be a part of the meta-analysis. Since the data from two earlier studies are included in their "Reappraisal" article, which was instrumental in discouraging further research for almost two decades, the updated information in that article was used. Of note, as pointed out by Cranton and Frackelton(7), the data showed positive results with some very sick patients, despite the title of the article.

Another study that qualified for this meta-analysis was that by Olszewer and Carter(40), which reported on 2482 patients that fit the criteria. Other patients in this study were omitted because they were not cardiovascular patients. Clarke and associates(25) provided the initial observations on EDTA for vascular problems in 1955. One of their followup papers(43) discussed objective data on individual patients. Casdorph(44,45) with two articles by himself and one with Farr(46) made significant contributions in the 80's. Godfrey(47) listed 27 patients in a letter to the New Zealand Medical Journal. Case studies by Morgan(48) and Brucknerova(49) met the criteria. Hancke and Flytlie(50) of Denmark provided EDTA chelation for patients who were on the waiting list for bypass or amputation, with the impressive results that 58 out of 65 bypass candidates and 24 out of 27 amputation candidates were able to cancel their surgery. In the same paper, which was reported at two European medical meetings, they described a larger series of coronary artery disease patients whose ST segments improved on exercise EKG's and peripheral vascular patients whose walking distances and ankle/brachial indices showed consistent gains with treatment. They also recorded symptomatic relief in as many as 92% of CAD patients, but the latter was excluded from the analysis because it was subjective. Their data were available but have not yet been published. The four studies that were included in the meta-analysis by McDonagh, Rudolph and Cheraskin(14,51-53)

utilized doppler ultrasound, oculocerebrovascular analysis and the A/B index to document improvement in carotid and peripheral circulation after treatment. McGillem and associates(4) provided a case report of a patient with severe coronary artery disease and renal problems that received low dose EDTA and failed to show improvement in his angiograms post-treatment. Van der Schaar(54), who is a cardiovascular surgeon from the Netherlands, conducted a particularly interesting calculation of the double and triple product to demonstrate increased exercise tolerance in chelated patients. The studies that were included in the meta-analysis are listed in Table 2.

Method of Analysis

The greater part of available research concerning the effect of EDTA chelation therapy on cardiovascular disease is of the pretest-posttest, without a control group, design. With this type of study the investigator measures the cardiovascular capability of each patient in a group before treatment, applies the treatment to each member of the group, and then measures the cardiovascular capability of each member of the group after treatment. The pretest, posttest data are then tabulated in some papers with statistical analysis, sometimes without.

Because of the lack of placebo controlled studies performed by researchers using EDTA chelation therapy, the efficacy of this technique has not spread widely into the medical community. To maintain scientific objectivity physicians require significant evidence that therapeutic efficacy exists before adopting any questionable therapy for use in their individual practice, and rightly so. Even though placebo control has, for the most part, been absent in existing EDTA studies, this does not mean that the data collected are not valid or useful. When a treatment effect is actually present, then the data used in a properly designed meta-analysis will show the presence and size of the effect whether the studies used are placebo controlled double-blind studies, or are pretest-posttest studies without control groups. This assumes, of course, that good design and measuring techniques are used and that the variables are not confounded.

Since significant statistical verification of the efficacy of EDTA therapy has not been demonstrated in many reports in the existing literature, this meta-analysis will use existing study data to provide this evidence. The procedure chosen is to determine the extent of the relationship, the "effect size", between EDTA chelation therapy and cardiovascular improvement. The correlation coefficient is the statistical descriptor selected for this meta-analysis because it indicates the degree of relationship between two variables. A correlation coefficient of 0.0 would indicate that there is no relationship between EDTA chelation therapy and improvement in cardiovascular capability, while a value of 1.0 would indicate a perfect relationship between the two variables. Variables with correlation coefficients greater than 0.7 are considered to be strongly related.

TABLE 2

Studies Used in Meta-Analysis

Author	Source/Date	Diagnoses	Test	Subjects	Improved	Same or Worse
Olszewer, Carter	M Hypoth/88	CAD, PVD, CVD	SEKG, Dplr, WD	2,482	2,379	103
Clarke	A J Med Sc/56	CAD	Exercise activ	20	19	1
Kitchell, et al	A J Card/63	Severe CAD	Ex Act/prolong life	38	23	15
Sloth-Nielson	A J Surg/92	PVD, Smokers	Arteriograms	30	2	28
Casdorph	J H Med/81	CVD	TECH99	15	14	1
Casdorph, Farr	J H Med/83	PVD/Gangrene	Avoid amputation	4	4	0
Casdorph	J H Med/81	ASHD	TECH99/EjFx	18	17	1
Olszewer, Carter	J N Med As/91	PVD	A/B index, W Dist	10	10	0
Godfrey	NZMJ/90	PVD	Doppler, A/B index	27	25	2
Morgan	J Adv Med/91	CAD	Stress EKG	2	2	0
Brucknerova	Cas Lekces/80	PVD	WD, arteriograms	2	2	0
Hancke	–/93	CAD, PVD	Avoid bypass/amput	92	82	10
Hancke	–/93	CAD	SEKG/STseg	253	175	78
Hancke	–/93	PVD	(A/B Index), W Dist	(262) 308	(217) 272	(45) 36
McGillem	NEJM/88	CAD, Renal Dis.	Angiograms	1	0	1
Rudolph, McDonagh	J Adv Med/90	CVD	Doppler/Ultrasound	1	1	0
McDonagh, et al	J Adv Med/82	CVD	Ocu CV Analysis	57	50	7
McDonagh, et al	J Adv Med/85	PVD	A/B Syst BP	117	95	22
Hoekstra, et al	–/93	PVD, CVD	Thermography	19,147	16,466	2,681
Van der Schaar	J Adv Med/89	CAD, CVD, PVD	Exercise Tolerance	111	111	0
Rudolph, et al	J Adv Med/91	CVD	Carotid Ultrasound	30	30	0
TOTAL-19 STUDIES				22,765	19,779 (87%)	2986 (13%)

There are two variables considered in this analysis; the method of treatment and the degree of improvement. Additionally, these two variables are conditioned to be discrete dichotomies. The method of treatment variable then is limited to the values, *EDTA chelation therapy* vs. *no therapy* and the degree of improvement variable is limited to the values of *significant cardiovascular improvement* vs. *no improvement or worse*. Formulating the variables in this way allows for the calculation of the phi(ϕ) coefficient, a special case of the Pearson r correlation coefficient when both variables are discrete dichotomies(55). After the phi(ϕ) correlation coefficients are calculated for the individual studies, the overall result of the meta-analysis is determined. The composite ϕ is a synthesis of the results of each of the individual studies. It is formulated by calculating a weighted average correlation coefficient where each individual study correlation used is weighted by the number of patients in the particular study(56).

Calculation of the phi(ϕ) correlation coefficient, as described for each individual study, implies that each study included in the meta-analysis was conducted in the following manner. The study subjects were pretested for some aspect of cardiovascular capacity. The treatment group was then treated with EDTA chelation therapy while treatment was withheld from an assumed control group. Both groups, the treatment group and the assumed control group, were then posttested on the same aspect of cardiovascular capacity. Sufficient data then exists to construct the 2×2 contingency table used for computing the phi(ϕ) correlation coefficient for that particular study.

Glass, McGaw and Smith(69) in their section on *Studies Without Control Groups* suggest that traditional or baseline values can be used as a "control" condition. They indicate that "experiments often have no untreated 'control' condition" but that "a control condition of no treatment can be defined and included". For the purpose of this meta-analysis, then, simply consider the existing study data to be the data for the treatment group and compare the improvement in cardiovascular function of the treatment group to a control group defined to have no improvement in cardiovascular capability.

It needs to be shown that the assumption of a no-treatment control group with no improvement is reasonable. This meta-analysis will use the blinded study by Olszewer, Sabbag and Carter(34) to show this. Their study is of particular interest to this meta-analytic procedure because the code was broken and as a consequence the data is in a particularly useful form. The specific data of interest are contained in TABLE 3 BLOOD PRESSURE INDEX of their paper, and are partially reproduced below.

To construct the contingency table a control group was hypothesized where

	Group Assigned to EDTA			Group Assigned to Placebo		
	Baseline	10 EDTA	20 EDTA	Baseline	10 Placebo	10 Placebo/ 10 EDTA
Rest	0.66	0.89	0.95	0.62	0.63	0.86
Exercise	0.54	0.78	0.88	0.56	0.54	0.75

the no-treatment control group was equal in size and other characteristics with the treatment group. It was assumed that there is no improvement with no treatment and data will be entered into the table to that effect. This may or may not be true. It is entirely possible that there might be improvement within the control group, even though treatment has been withheld. Some studies are more likely than others to show an improvement for no treatment. An examination of the Olszewer, Sabbag and Carter data(34) indicates that there was essentially no change in placebo subject function whereas there was a significant change in EDTA subject function over 10 treatments. This can indicate one of two possibilities, either the placebo is having no effect or the placebo-treated subjects might not be responding to any treatment, either placebo or EDTA. The second scenario is rejected because the response of the placebo subjects showed an improvement when EDTA was substituted for the placebo for the remaining 10 infusions. Therefore, it is concluded that for similar populations using the EDTA chelation therapy protocol the assumption of a no-improvement control group is valid.

As an example, suppose that a particular study indicates that 15 out of 20 patients had evidence of a significant improvement in cardiovascular capability after the EDTA treatment protocol while 5 patients showed no improvement. Note that for the "no treatment" or "control" group the posttest value equals the pretest value for "no improvement" and the corresponding table entries are thus (0,20). For the "treatment" group it is clear that the table entries are (15,5). The 2×2 contingency table and corresponding ϕ correlation coefficient is given below.

	Improvement	No improvement	TOTALS
Control (no treatment)	0	20	20
EDTA treatment	15	5	20
TOTALS	15	25	40

The ϕ correlation coefficient calculation is;

$$\phi = \frac{(15)(20) - (0)(5)}{[(20+0)(15+5)(0+15)(20+5)]^{1/2}} = 0.77$$

which indicates a high correlation. With a high correlation it can be stated that there is a positive relationship between EDTA chelation therapy and improvement in cardiovascular function. Traditionally, the square of the coefficient of correlation or the coefficient of determination is used as an estimate of the shared variance between the two variables(57).

For correlation interpreting purposes Table 3 can be used as a guide.

Hinkle, Wiersma & Jurs(55) provide guidelines for interpreting the size of a correlation coefficient, which are listed in Table 4.

The following formula is used to calculate a composite correlation coefficient. The i_{th} study has N_i subjects with correlation coefficient ϕ_i. The com-

TABLE 3

Group size	Improvement	No improvement	Ø
20	20	0	1.00
20	15	5	0.77
20	5	15	0.38
20	0	20	0.00

TABLE 4

Interpreting the Size of a Correlation Coefficient (Hinkle, Wiersma & Jurs)

.90 to 1.00	Very high positive correlation
.70 to .90	High positive correlation
.50 to .70	Moderate positive correlation
.30 to .50	Low positive correlation
.00 to .30	Little if any correlation

posite correlation, $\phi_{composite}$ represents the relationship between improvement in cardiovascular activity and EDTA chelation therapy taking data from all of the studies into account. The effect of each individual study is weighted by the number of patients in the study. A 10 subject study has about 1/10th the weight of a 100 subject study.

$$\phi_{composite} = \frac{\Sigma N_i \phi_i}{\Sigma N_i}$$

Results

Table 5 shows those studies included in the meta-analysis, indicating the individual correlation coefficient for each study and the overall correlation coefficient. The overall correlation coefficient is equal to 0.88. This value indicates a highly positive correlation between EDTA chelation therapy and improvement in cardiovascular func-

TABLE 5

Correlation Coefficient for All Studies

Author	Subjects	Improved	Same/Worse	Correlation
Olszewer, Carter	2,482	2,379	103	0.96
Clarke	20	19	1	0.95
Kitchell, et al	38	23	15	0.66
Sloth-Nielson	30	2	28	0.19
Casdorph	15	14	1	0.94
Casdorph, Farr	4	4	0	1.00
Casdorph	18	17	1	0.95
Olszewer, Carter	10	10	0	1.00
Godfrey	27	25	2	0.93
Morgan	2	2	0	1.00
Brucknerova	2	2	0	1.00
Hancke	92	82	10	0.90
Hancke	253	175	78	0.73
Hancke	308	272	36	0.89
McGillem	1	0	1	0.00
Rudolph, McDonagh	1	1	0	1.00
McDonagh, et al	57	50	7	0.88
McDonagh, et al	117	95	22	0.83
Hoekstra, et al	19,147	16,466	2,681	0.87
Van der Schaar	111	111	0	1.00
Rudolph, et al	30	30	0	1.00

Overall Correlation Coefficient = 0.88

tion. The traditional interpretation of using the square of the correlation coefficient as an estimate of the variability between the two variables indicates that approximately 77% of the variability in improvement in cardiovascular function is associated with the treatment of EDTA chelation therapy. The remaining 23% is associated with other unknown factors. Wolfe(56) indicates that Rosenthal and Rubin provide an alternate "insightful" way to appraise the significance of correlation coefficients with their "binomial effect size display" (BESD) for 2×2 contingency tables. For our variables, the BESD is the *estimated* difference in success rate between the two variables, EDTA

TABLE 6

	Improvement	No improvement	Total
Control (No Treatment)	6	94	100
EDTA Treatment	94	6	100
TOTAL	100	100	200

chelation therapy and improvement in cardiovascular function. That is, for a correlation coefficient of 0.88 we would expect an increase of success in cardiovascular improvement from 6% of patients improved with no treatment to 94% of patients improved as a result of applying EDTA chelation therapy. The Binomial Effect Size Display illustrating this condition is shown in Table 6. Note that the correlation coefficient calculated for the data of this table is .88. The formula used for calculating the success rate is:

$$\text{Success Rate} = .50 \pm \phi /2$$

Tables 7 and 8 demonstrate that there is little difference in the correlation coefficient whether the analysis is limited to large studies or to small studies.

Mechanism of Action

Gordon and Vance(58), Halstead(59) and Cranton and Frackelton(7) have reviewed the pharmacology of EDTA in the treatment of cardiovascular disease. Emphasis was placed(7) on reduction of free radicals by removing heavy metals, iron and copper and by antioxidant activity. Bjorksten(60) suggested that chelation might be valuable in life extension. Deucher(61) described chelation as an "antioxidant strategy", and Gutteridge(62) identified increased effectiveness of hydroxyl-radical scavengers in the presence of EDTA. An editorial by Zylke(63) mentioned edetic acid (EDTA) as a possible treatment to control oxygen radicals. Kaman, Rudolph, McDonagh and Walker(64) demonstrated the removal of metastatic calcium in rabbit aortas. Kindness and Frackelton(65) showed the beneficial therapeutic effects of EDTA chelation of inhibiting platelet aggregation and pro-

TABLE 7

Small Studies Only

Author	Subjects	Improved	Same/Worse	Correlation
Clarke	20	19	1	0.95
Kitchell, et al	38	23	15	0.66
Sloth-Nielson	30	2	28	0.19
Casdorph	15	14	1	0.94
Casdorph, Farr	4	4	0	1.00
Casdorph	18	17	1	0.95
Olszewer, Carter	10	10	0	1.00
Godfrey	27	25	2	0.93
Morgan	2	2	0	1.00
Brucknerova	2	2	0	1.00
Hancke	92	82	10	0.90
Hancke	253	175	78	0.73
Hancke	308	272	36	0.89
McGillem	1	0	1	0.00
Rudolph, McDonagh	1	1	0	1.00
McDonagh, et al	57	50	7	0.88
McDonagh, et al	117	95	22	0.83
Van der Schaar	111	111	0	0.00
Rudolph, et al	30	30	0	1.00

Overall Correlation Coefficient = 0.84

TABLE 8

Large Studies Only

Author	Subjects	Improved	Same/Worse	Correlation
Olszewer, Carter	2,482	2,379	103	0.96
Hoekstra, et al	19,147	16,466	2,681	0.87

Overall Correlation Coefficient = 0.88

longing the partial thromboplastin time. Lamb and Leuke(66) recently discussed the concentration required in vitro for EDTA to inhibit the oxidation of LDL by macrophages and by copper. An excellent compendium of articles, including the protocol recommended by the American College for Advancement in Medicine for EDTA administration, was published in A Textbook of EDTA Chelation Therapy in 1989(67).

Discussion

Lugo-Miro and associates(68) suggested that meta-analysis is one of the best tools to evaluate controversial therapies. This paper has utilized a similar technique to estimate the statistical relationship between EDTA chelation therapy and the positive effect that the therapy has on atherosclerotic cardiovascular disease. The results show a high positive correlation, indicating its efficacy.

More than 40 published reports and two unpublished studies have been examined in this paper. Only one multi-patient study(35), which was conducted by Danish vascular surgeons, contained data that showed negative results. The trials by Diehm(38) and Kitchell and associates(42) both demonstrated favorable clinical outcomes, in spite of negative conclusions. Nineteen studies met the criteria and were included in the analysis. The meta-analysis thus contained results from the treatment of 22,765 patients, 87% of whom had favorable outcomes. This percentage is changed very little whether the large studies by Olszewer and Carter and by Hoekstra and associates are included or not.

Only those improvements measurable by an objective test were accepted as evidence of a favorable outcome. Those patients who improved clinically but did not improve their objective test results were placed in the category of the same, or worse.

One problem with assessing therapeutic modalities is that negative data are sometimes not published. Glass, McGaw and Smith(69) indicate that the selection of papers may bias a meta-analysis. To minimize this bias potential, the authors are in the process of collecting additional data.

The majority of studies considered functional assessments of the patients. Sloth-Nielson and associates(35) relied on arteriograms, which may have ignored improvements in small vessel blood flow.

Several studies demonstrated that maximal improvement with EDTA therapy occurred up to three months or more after the basic course of therapy was completed. Reasons for this effect are unknown. Possible explanations include a delayed antioxidant effect, a gradual restoration of depleted trace minerals or that causative metals, acting as free radical catalysts, are removed, thus allowing a natural healing process to occur over time.

The safety of EDTA treatment has been acknowledge by the FDA in the Foundation Partners trial, and no further studies were required to demonstrate safety under the IND. Our literature search revealed no significant concerns for safety, as long as the published protocol(67) is carefully followed. Reports of toxicity(70,71) involved the rapid daily administration of a much higher dose of EDTA than is allowed in the protocol.

In 1984, the American College of Advancement in Medicine estimated that 400,000 patients had been treated by member physicians with no fatalities attributed to the recommended protocol(72). The number of patients treated safely has probably doubled since that time.

Recently, the Great Lakes Association of Clinical Medicine released a white paper on The Cost Effectiveness of Alternative Medicine in the Workplace(73). The chapter on EDTA chelation made a case for consideration of this therapy as an alternative or adjunct to bypass surgery and angioplasty as a cost saving measure.

Conclusion

This meta-analysis offers very strong evidence that EDTA is effective in the treatment of cardiovascular disease. A number of studies are in the planning stage, but have not been activated for lack of financial support. The authors hope that this statistically significant meta-analysis might speed this support. Interest is growing in New Zealand, Canada, Great Britain, Denmark, Brazil and other countries. EDTA therapy needs to assume its place in the treatment of cardiovascular disease.

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