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EDTA Chelation Treatment for Vascular Disease: A Meta-Analysis Using Unpublished Data

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ABSTRACT: The authors previously reported the results of a meta-analysis on the correlation between EDTA therapy and improvement in cardiovascular function where only published data were used in the analysis(1). Many analysts suggest that using exclusively published data in a meta-analysis leads to a lowered confidence level in the results because of the possibility of publication bias. In order to improve the confidence level if possible in the results of their original paper the authors repeated the study using unpublished data. Unpublished "file drawer" data were collected from 32 clinicians who utilize intravenous EDTA with essentially the same protocol as was used in the original study. Various objective measurements demonstrated improvement in 1086 or 88% of the 1241 patients reported with an overall correlation coefficient of 0.88. A comparison of the studies using unpublished data with published data shows that the results are essentially the same. These data provide additional confidence of the effectiveness of EDTA treatment.

Background

Intravenous EDTA with trace minerals and vitamins has been used in conjunction with lifestyle changes to treat vascular disease by a growing number of physicians. The authors conducted a meta-analysis(1) that showed a high positive correlation between treatment

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with EDTA and improvement in vascular disease. Included in the meta-analysis were 18 published articles and one large study that had been submitted for publication. All of the studies included in the meta-analysis met the criteria that there were data on individual patients and that objective testing was utilized in measuring outcomes.

Of the 22,765 patients analyzed, 19,779 or 87% showed measurable improvement after treatment. The overall correlation coefficient was 0.88. A meaningful interpretation of a correlation coefficient using Rosenthal and Rubin's binomial effect size display(1) is that 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 original meta-analysis, as conducted, offered very strong evidence of the effectiveness of EDTA chelation therapy in the treatment of cardiovascular disease.

A Bias Criticism of Meta-Analysis

One of the criticisms of meta-analysis is that when only published data is used in the analysis, there is potential for a type I publication error to exist. A type I error is the rejection of the null hypothesis when it is in fact true. For our case the null hypothesis is "EDTA chelation therapy does not improve cardiovascular function". The basic premise regarding this criticism of meta-analysis is that there is a tendency to publish only positive or significant results and that results that are not significant remain unpublished. This is sometimes called the "File Drawer Problem"(2). One of two approaches can be used when addressing the possibility of a type I publication error. Either estimate the number of additional studies with nonsignificant results needed to nullify the significant result of the published data, or acquire unpublished data and include or compare the unpublished results with the published results. If the two results are significantly different then the result of the original analysis is suspect and the difference between the two needs to be resolved.

Cook and associates(3) recently wrote about the importance of the inclusion of unpublished data when performing a meta-analysis, especially when evaluating controversial medical therapies. Additionally, Wolf(4) in his "Guidelines for Practice" recommends that those researchers conducting a meta-analysis "search for unpublished studies in order to test for a type I error publication bias". In order to address

the question regarding the validity of the results of our original paper, i.e. the existence of a type I publishing error, the authors decided to search for unpublished data in order to make a comparison between published data results and unpublished data results. Additional unpublished data were solicited by asking members of the American College for Advancement in Medicine (ACAM) to submit unpublished data from their individual medical practices. This paper reports and analyzes the results of this effort.

Unpublished Data Limitation

There are several problems to consider in the search for unpublished data for inclusion in a meta-analysis. Two of the more serious problem areas are obtaining a representative data set and the acquisition of good data. An unpublished data set is representative when the data come from a sample of the population equivalent to the population of the original meta-analysis. Data are good where adequate control conditions exist. Control of data is adequate when existing threats to internal and external validity and reliability are minimized. Those who argue against the inclusion of unpublished data without peer review in an analysis typically indicate that peer review in the publication process is meant to protect the reader from substandard material or inadequate data. Peer review is used to insure that those papers included in the publication meet certain minimum standards. Bypassing the peer review process by using unpublished data allows for the possibility of erroneous conclusions to be made because of the introduction of substandard data.

Being cognizant of these dangers the authors collected additional unpublished data from practitioners of EDTA chelation therapy. The advantage of using unpublished data from this source has the following benefits. The sample data set is selected from a population which approximates the sample from the population of the original meta-analysis. The integrity of the individual data sets across the different study sets with respect to both validity and reliability is high for the following reasons. The protocol used in EDTA chelation therapy has been standardized, although minor variations are allowed, and physicians who administer the EDTA treatment have all been trained and certified to use the protocol. For objective data collection, the test procedures, equipment used, and interpretation of results for EDTA chelation therapy are all standard in the general practice of medicine

and are accepted by practitioners in the field. No obscure or unusual protocols are needed in the administration of EDTA chelation therapy.

Method of Data Acquisition and Reduction

Two letters of solicitation were written and three requests from the podium at national meetings were made to the membership of ACAM requesting unpublished data. Data type was limited to the results of treating vascular disease with EDTA chelation therapy. The criteria for data collection were as follows:

1. Consecutive patients with objective testing done before and after treatment were to be included.
2. All patients must have had vascular disease with such diagnoses as coronary artery disease, peripheral vascular disease and/or cerebral vascular disease specified.
3. Treatment given was required to be according to the published protocol(5) that all members agree to use. The protocol includes 20-30 treatments of intravenous EDTA with specified additives, oral nutritional supplements, and lifestyle changes as needed.
4. Well-accepted, objective testing was required to show whether each patient improved or not with treatment.
5. Published data were excluded.

The data were then tabulated. Correlation coefficients were calculated for each investigator and for the entire collection of unpublished data. For comparison purposes correlation coefficients were also included for only published data and for the entire collection including both published and unpublished data.

The correlation coefficients were calculated in the following manner. There are two variables considered in this analysis. The first is the method of treatment and the second is 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. little or 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

TABLE 1

Correlation Coefficient Data for Unpublished Studies
Overall Correlation Coefficient = 0.88

Author	Type Study	Subjects	Improved	Same/ Worse	Correlation
Garg	B,D,F,H	32	31	1	0.97
Hart	B,D,F,H	7	7	0	1.00
Hodara	B,D,F,H	1	1	0	1.00
Janson	B,D,F,H	10	7	3	0.73
Laird	B,D,F,H	19	12	7	0.68
Affandi	B,D,F,H	10	10	0	1.00
Bock	B,D,F,H	11	10	1	0.91
Born	B,D,F,G	748	645	103	0.87
Darbro	B,D,F,H	10	10	0	1.00
Goldberg	B,D,F,H	4	3	1	0.77
Gonzalez	B,D,F,H	3	3	0	1.00
Gunter	B,D,F,H	7	6	1	0.87
Eckerly,Dole	B,D,F,H	19	19	0	1.00
Harris	B,D,F,H	1	1	0	1.00
Maulfair	B,D,F,H	9	8	1	0.89
Penwell	B,D,F,H	49	42	7	0.87
Reynoso	B,D,F,H	8	8	0	1.00
Chappell	B,D,F,H	33	27	6	0.83
Sams	B,D,F,H	18	18	0	1.00
Magaziner	B,D,F,H	1	1	0	1.00
Speckhart	B,D,F,H	1	1	0	1.00
Young	B,D,F,H	35	32	3	0.92
Braverman	B,D,F,H	1	1	0	1.00
Rozema	B,D,F,G	53	50	3	0.94
Kindness	B,D,F,H	29	26	3	0.90
DeSouza	B,D,F,H	9	9	0	1.00
Moharram	B,D,F,H	1	1	0	1.00
Olzsewer, et al.	B,D,F,H	30	26	4	0.87
Godfrey	B,D,F,H	16	16	0	1.00
Levin	B,D,F,H	22	15	7	0.72
Wolverton	B,D,F,H	21	19	2	0.91
Walker	B,D,F,H	23	21	2	0.92
	TOTALS	1241	1086	155	

Study types: A-No lifestyle changes, B-Lifestyle changes, C-Published data, D-Unpublished data, E-Large studies, F-Small studies, G-1.5 gm dose, H-3.0 gm dose

TABLE 2

Data from Unpublished Studies Used in Meta-Analysis

Doctor	Location	Diagnoses	Objective Test	Subjects	Improved	Same/Worse
GARG	LONDON, ENGLAND	ASHD,PVD, CAROTID INSUF	ANGIOGM(15), DOPPLERS(31)	32	31	1
HART	SPOKANE, WASH	PVD,CAD,CVD,HBP	DOPPLER, EKG,BP,CHOL, WDIST	7	7	0
HODARA	BRAZIL	CAD,CVD	EKG,ULTRASOUND	1	1	0
JANSON	CAMBRIDGE, MA	CAD	CHO, TRIG,NEED FOR MED	10	7	3
LAIRD	LEICESTER, NC	PVD	DOPPLER	19	12	7
AFFANDI	INDONESIA	CAD,CVD	SEKG,EKG,EMG, BP,CHOL	10	10	0
BOCK	RHINEBECK, NY	PVD,CAD,CVD	SEKG,EKG,DPLR, CULTSD	11	10	1
BORN	GRAND RAPIDS, MI	CAD,PVD,CVD	DPLR, EKG,CARDIOINTEGRAPH	748	645	103
DARBRO	INDIANAPOLIS, IN	ASHD	SMAC 24	10	10	0
GOLDBERG	DAYTON, OH	CAD, HYPERLIPIDEMIA	CHOL, TRIG, REPEAT BYPASS	4	3	1
GONZALEZ	HOMOSASSA, FL	CAD,PVD	SEKG,DPLR,CHOL	3	3	0
GUNTER	CAMILLA, GA	PVD,CAD,CVD	DOPPLER	7	6	1
ECKERLY,DOLE	PLYMOUTH, MN	PVD,CAD,CVD,HBP	DOPLR,BP,COG FUNCTION	19	19	0
HARRIS	ISLAND HEIGHTS, NJ	GANGRENE	HEALED	1	1	0
MAULFAIR	MERTZTOWN, PA	PVD,RAYNAUDS, CAD,CVD	DOPPLER,STR EKG	9	8	1
PENWELL	LINDEN,MI	CAD(21),CVD(3),	HM,EKG,STR	49	42	7

		PVD(25)	EKG,DPLR,XSUR			
REYNOSO	MANILA	CAD,PVD	CATH(3),DOPPLER	8	8	0
CHAPPELL	BLUFFTON, OH	PVD,CVD	DOPPLER	33	27	6
SAMS	COLUMBUS, MS	CVD, PVD	DOPPLER	18	18	0
MAGAZINER	CHERRY HILL, NJ	CVD	CAROTID ULTRA-SOUND	1	1	0
SPECKHART	NORFOLK, VA	CAD	STRESS THALIUM	1	1	0
YOUNG	SALEM, OR	CVD,CAD,PVD	DOPPLER, HOLTER,EKG, CHOL	35	32	3
BRAVERMAN	SKILLMAN, NJ	CAD	PET SCAN	1	1	0
ROZEMA	LANDRUM, SC	PVD	DOPPLER	53	50	3
KINDNESS	BLUFFTON, OH	HYPERLIPIDEMIA	APOLIPOPROTEINS	29	26	3
DE SOUZA	BRAZIL	CAD,PVD,CVD,HBP	ANGIOGM(3),EKG, DOPPLER	9	9	0
MOHARRAM	SANTA BARBARA, CA	CAD	BYPASS NEEDED	1	1	0
OLZSEWER, ET AL.	BRAZIL	CAD	STRESS EKG	30	26	4
GODFREY	NEW ZEALAND	PVD,CAD	DPLR,STRESS	16	16	0
LEVIN	NEW YORK, NY	CAD,PVD,CVD	EKG,MED NEEDED S EKG,HM,EKG, PVR,DOPPLER	22	15	7
WOLVERTON	CLARKSVILLE, IN	PVD,CAD,CVD,	ANGIOGM(2),S EKG, EKG,DPLR	21	19	2
WALKER	ST LOUIS, MO	CAD,CVD	CAROTID UL-TRSD,ACTIVITY TOL	23	21	2
			TOTALS	1241	1086 (88%)	155 (12%)

both variables are discrete dichotomies. 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. The details and assumptions of this method of data reduction were published(1).

Results

As is shown in Table 1, thirty-two physicians provided data on 1241 patients, 1086 of them (88%) had measurable improvements by objective testing. Even though the inclusion of the several studies consisting of "one" patient can be statistically criticized, we have chosen to include them to show the robustness of the therapy. We also note that the correlation coefficient is the same with and without the studies of "one" patient. The overall correlation coefficient between treatment with EDTA and improvement in vascular disease was 0.88, which is a high positive correlation. Table 2 shows the testing and results of each doctor who provided data. Table 3 indicates that for the collection of all studies, published and unpublished, the overall correlation coefficient is 0.88. Table 4, the original meta-analysis results, shows that the overall correlation coefficient for the set of published studies is also 0.88. Since the correlation coefficient of 0.88 is the same for both the published and unpublished data, we conclude that there is no type I publication error. Our trust in the statement that "there is significant cardiovascular improvement associated with the treatment of EDTA chelation therapy" is much stronger as a result of this follow up meta-analysis using unpublished data.

Discussion

The results of this collection of unpublished data correspond remarkably well with the meta-analysis of published and prepublication studies. Both sets of data reflect a high correlation between improvement in cardiovascular function and treatment with EDTA. The largest published series to date was the 2870 patients reported by Olzsewer and Carter(6). All of these reports show that at least 87% of vascular patients show measurable improvement with EDTA treatment.

TABLE 3

Correlation Coefficient Data for all Studies
Overall Correlation Coefficient =0.88 "All Data"

Author	Type Study	Subjects	Improved	Same/ Worse	Correlation
Olzsewer,Carter	B,C,E,H	2482	2379	103	0.96
Clarke	A,C,F,H	20	19	1	0.95
Kitchell, etal	A,C,F,H	38	23	15	0.66
Sloth-Nielson	B,C,F,H	30	2	28	0.19
Casdorph	B,C,F,H	15	14	1	0.94
Casdorph, Farr	B,C,F,H	4	4	0	1.00
Casdorph	B,C,F,H	18	17	1	0.95
Olzsewer,Carter	A,C,F,G	10	10	0	1.00
Godfrey	B,C,F,H	27	25	2	0.93
Morgan	B,C,F,H	2	2	0	1.00
Brucknerova	A,C,F,H	2	2	0	1.00
Hancke	B,C,F,H	92	82	10	0.90
" "	B,C,F,H	253	175	78	0.73
" "	B,C,F,H	308	272	36	0.89
McGillem	B,C,F,H	1	0	1	0.00
Rudolph, McDon	B,C,F,H	1	1	0	1.00
McDonagh, et al	B,C,F,H	57	50	7	0.88
McDonagh, et al	B,C,F,H	117	95	22	0.83
Hoekstra, et al	B,D,E,H	19147	16466	2681	0.87
Van der Schaar	B,C,F,H	111	111	0	1.00
Rudolph, etal	B,C,F,H	30	30	0	1.00
Garg	B,D,F,H	32	31	1	0.97
Hart	B,D,F,H	7	7	0	1.00
Hodara	B,D,F,H	1	1	0	1.00
Janson	B,D,F,H	10	7	3	0.73
Laird	B,D,F,H	19	12	7	0.68
Affandi	B,D,F,H	10	10	0	1.00
Bok	B,D,F,H	11	10	1	0.91
Born	B,D,F,G	748	645	103	0.87
Darbro	B,D,F,H	10	10	0	1.00
Goldberg	B,D,F,H	4	3	1	0.77
Gonzalez	B,D,F,H	3	3	0	1.00

TABLE 3 *Continued*

Author	Type Study	Subjects	Improved	Same/ Worse	Correlation
Gunter	B,D,F,H	7	6	1	0.87
Eckerly,Dole	B,D,F,H	19	19	0	1.00
Harris	B,D,F,H	1	1	0	1.00
Maulfair	B,D,F,H	9	8	1	0.89
Penwell	B,D,F,H	49	42	7	0.87
Reynoso	B,D,F,H	8	8	0	1.00
Chappell	B,D,F,H	33	27	6	0.83
Sams	B,D,F,H	18	18	0	1.00
Magaziner	B,D,F,H	1	1	0	1.00
Speckhart	B,D,F,H	1	1	0	1.00
Young	B,D,F,H	35	32	3	0.92
Braverman	B,D,F,H	1	1	0	1.00
Rozema	B,D,F,G	53	50	3	0.94
Kindness	B,D,F,H	29	26	3	0.90
DeSouza	B,D,F,H	9	9	0	1.00
Moharran	B,D,F,H	1	1	0	1.00
Olzsewer, et al	B,D,F,H	30	26	4	0.87
Godfrey	B,D,F,H	16	16	0	1.00
Levin	B,D,F,H	22	15	7	0.72
Wolverton	B,D,F,H	21	19	2	0.91
H. Walker	B,D,F,H	23	21	2	0.92
TOTALS		24006	20865	3141	

Study types: A-No lifestyle changes, B-Lifestyle changes, C-Published data, D-Unpublished data, E-Large studies, F-Small studies, G-1.5 gm dose, H-3.0 gm dose

All of the 32 clinicians whose work is described in this paper used the ACAM protocol for treatment of various vascular diseases. As noted in Tables 1 and 4, most of the data sets contained lifestyle changes, but there were a few in the original meta-analysis which did not. Although the correlation coefficients in the no lifestyle change data sets were also high, the numbers were too small to draw additional conclusions. One of the contributors in the original meta-analysis and two in this unpublished group used a lesser dose of 1.5 grams of EDTA rather than the usual dose of 3 grams. It is beyond the scope

TABLE 4

Correlation Coefficient Data for Published Studies
Overall Correlation Coefficient = 0.88

Author	Type Study	Subjects	Improved	Same/ Worse	Correlation
Olzsewer,Carter	L,C,E,H	2482	2379	103	0.96
Clarke	A,C,F,H	20	19	1	0.95
Kitchell, et al	A,C,F,H	38	23	15	0.66
Sloth-Nielson	B,C,F,H	30	2	28	0.19
Casdorph	B,C,F,H	15	14	1	0.94
Casdorph, Farr	B,C,F,H	4	4	0	1.00
Casdorph	B,C,F,H	18	17	1	0.95
Olzsewer,Carter	A,C,F,G	10	10	0	1.00
Godfrey	B,C,F,H	27	25	2	0.93
Morgan	B,C,F,H	2	2	0	1.00
Brucknerova	A,C,F,H	2	2	0	1.00
Hancke	B,C,F,H	92	82	10	0.90
" "	B,C,F,H	253	175	78	0.73
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McGillem	B,C,F,H	1	0	1	0.00
Rudolph, McDon	B,C,F,H	1	1	0	1.00
McDonagh, et al	B,C,F,H	57	50	7	0.88
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Hoekstra, et al	B,D,E,H	19147	16466	2681	0.87
Van der Schaar	B,C,F,H	111	111	0	1.00
Rudolph, et al	B,C,F,H	30	30	0	1.00

Study types: A-No lifestyle changes, B-Lifestyle changes, C-Published data, D-Unpublished data, E-Large studies, F-Small studies, G-1.5 gm dose, H-3.0 gm dose

of this paper to compare the two doses, but the subset correlation coefficients were essentially the same and this did not affect the overall results.

The tests performed by each physician varied, but they were similar and commonly accepted. There were also minor variations in the type of nutritional supplements used.

The results of this paper confirm the effectiveness of EDTA chelation therapy in the treatment of cardiovascular disease.

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