ORIGINAL RESEARCH ARTICLE

Evid Based Integrative Med 2005; 2 (1): 27-35
1176-2330/05/0001-0027/$34.95/0

Subsequent Cardiac and Stroke Events in Patients with Known Vascular Disease Treated with EDTA Chelation Therapy

A Retrospective Study

L. Terry Chappell,[1] *Rakesh Shukla,*[2] *Jun Yang,*[2] *Rene' Blaha,*[3] *Tammy Born,*[4] *Claus Hancke,*[5] *William Mitchell,*[6] *Efrain Olszewer,*[7] *Peter van der Schaar*[8] and *James Ventresco*[9]

1 Private Practice, Bluffton, Ohio, USA
2 Center for Biostatistical Services, University of Cincinnati Medical Center, Cincinnati, Ohio, USA
3 Private Practice, Trillium Health Center, Lancaster, Ohio, USA
4 Private Practice, Grand Rapids, Michigan, USA
5 Private Practice, Lyngby, Denmark
6 Private Practice, Powell, Ohio, USA
7 Private Practice, Sao Paulo, Brazil
8 Private Practice, Leede, The Netherlands
9 Deceased. Formerly in Private Practice, Youngstown, Ohio, USA

Abstract

Context: Myocardial infarction (MI) and strokes are leading causes of death in the US. Surgical and medical treatments can be helpful, but carry risks of morbidity and mortality.

Objective: To evaluate whether cardiac events were reduced for patients with known vascular disease who were treated with intravenous ethylene diamine tetra-acetic acid (EDTA) chelation therapy.

Design: Retrospective study with a 3-year follow-up, compared with similar patient groups by use of meta-analysis.

Population and setting: A total of 220 consecutive patients with known vascular disease were treated with chelation therapy during 1992–2001. Eight outpatient centres were included: five from the US and one each from Denmark, the Netherlands and Brazil. Average patient age was 64 years, 72.3% were males and 18.2% were smokers. Average number of treatments was 58.

Main outcome measures: MI, stroke and death from any cause were primary outcome measures. Secondary measures were resolution of symptoms and need for coronary artery bypass surgery (CABG) and percutaneous transluminal coronary angioplasty.

Results: According to the meta-analysis, expected outcomes in a 3-year follow-up period for 220 patients with coronary artery disease treated only with conventional therapies would be 15 MIs and six deaths. There were no deaths and no MIs in this group of patients who received chelation therapy. Four patients had strokes but recovered well. There were two angioplasties and six CABG procedures. Compared with similar patient populations treated with conventional therapies, patients who also were chelated had a 93.6% lesser need for angioplasty and a 62.5% reduced need for CABG. Of the patients that initiated treatment with symptoms, 68.7% had complete resolution of symptoms.

Conclusions: This study indicates that the administration of intravenous EDTA chelation therapy for patients with vascular disease resulted in fewer subsequent cardiac events than primary treatment with CABG, angioplasty or conventional medical therapy. EDTA chelation therapy for vascular disease is a reasonable,

off-label adjunct, especially for patients who refuse or are not eligible for surgery. Clinical trials such as the Trial to Assess Chelation Therapy (TACT) are needed for definitive proof.

Treatment of vascular disease with ethylene diamine tetra-acetic acid (EDTA) chelation therapy has been controversial for 50 years. The major reason for controversy is that no large-scale clinical trials with sufficient power have been published.[1] Many editorials and opinion articles have been published, most of which have had negative conclusions. Recently, there has been increased interest in the effects of EDTA chelation therapy because Lin et al.[2] demonstrated that renal function in patients with kidney failure can be improved with EDTA and Nash et al.[3] showed that hypertension in females is directly related to their lead burden.

Proponents of chelation therapy for the treatment of vascular disease have published numerous case studies and uncontrolled trials that have seemed to indicate clinical improvement.[4] Olmstead's detailed monograph on the subject concluded that the preponderance of the evidence was in favour of apparent improvement for patients with peripheral and coronary artery disease but inadequate to show a trend for carotid disease.[5] He called for large clinical trials to establish proof. Chappell and Stahl[6] published a meta-analysis that demonstrated a 0.88 correlation coefficient between treatment with EDTA and improvement in vascular disease that was documented in published studies by objective testing. Hancke and Flytlie[7] treated 65 patients on the waiting list for coronary artery bypass surgery (CABG), and 58 were able to cancel their surgery. Similarly, they treated 27 patients on the waiting list for amputation, and 24 limbs were saved after EDTA treatment. Hancke[8] reported on a 6–12-year follow-up on the patients with peripheral vascular disease. The vast majority of them were alive and doing well, with their legs intact.

Controlled clinical trials were published by teams headed by Guldager,[9] van Rij[10] and Knudtsen,[11] with some of the data demonstrating small improvements that were not statistically significant. The former two examined peripheral vascular disease and Knudtsen studied coronary artery disease. None of these trials was large enough to draw definitive conclusions. Letters to the editor criticised the procedures and conclusions of all three. The stated conclusions of all three trials were that EDTA chelation therapy was ineffective. These trials did not indicate high risks or a high incidence of adverse events from the therapy.

The endpoints of these three controlled trials were test results and performance measures such as walking distance and exercise electrocardiograms.[9-11] Research results with such measures are often variable. None of the research to date has evaluated cardiac events for patients treated with EDTA, although an incidental finding in the Knudtsen study[11] revealed four angioplasties performed in the placebo group and none in the EDTA treatment group.

In 2003, Lamas began a prospective, 5-year, randomised, double-blind, controlled, multicentre clinical trial funded by the National Institutes of Health and the National Center of Complementary and Alternative Medicine with 2372 subjects who had previous myocardial infarctions (MIs): the Trial to Assess Chelation Therapy (TACT) study (http://nccam.nih.gov/chelation).[12] The treatment group is receiving an ample course of 40 treatments with EDTA chelation therapy. The primary endpoints are cardiac events. Investigators for this trial include university professors, cardiologists and experienced chelation practitioners.

This article reports on a retrospective study of 220 patients with documented vascular disease, also looking at cardiac events as endpoints. Our objective was to evaluate whether cardiac events were reduced for patients with known vascular disease who were treated with intravenous EDTA chelation therapy.

Methods

Study Design and Participants

The study was evaluated by two institutional review boards and carried out with the ethical standards set forth in the Helsinki Declaration of 1975.

Eight physicians in private practice who were experienced in providing intravenous EDTA chelation therapy agreed to participate in the study. An office nurse of each physician worked alone or with the research assistant to define patients who might be eligible for the study on the basis of being treated with at least 20 treatments of intravenous EDTA chelation therapy during the period 1992–2001. Patients gave informed consent for the use of the data from their charts. Nurses and technicians from the offices of the three physicians from the countries of Denmark, the Netherlands and Brazil extracted the data from clinical charts. For the five physician offices in the US, the same research technician travelled to all offices to extract the data. It was determined whether the patients met the inclusion criteria and did not meet the exclusion criteria. The research assistant made follow-up telephone calls to patients to check on some of the data.

The same report form was used for all patients. If the relevant data on the final report form for a patient were incomplete, that patient was excluded from the study. All patients were treated according to the published protocol established by the American

Board of Clinical Metal Toxicology and the American College of Advancement in Medicine (ACAM).[4] All physicians were trained by either ACAM or by the International College of Integrative Medicine, and were experienced in administering the treatments accurately and safely.

The inclusion criteria were that patients had to have documented vascular disease and they had to have been treated with at least 20 treatments of intravenous EDTA chelation therapy during the study period. Acceptable documentation to establish vascular disease included a past history of a least one cardiac event or a distinctly abnormal vascular test result. Cardiac events were defined as MI, stroke, CABG and angioplasty. Abnormal vascular testing included Doppler ultrasound testing indicating a blockage of >50% of a major artery, abnormal cardiac catheterisation and abnormal exercise or resting electrocardiograms indicating ischaemia.

The exclusion criterion was insufficient follow-up data to determine if the patient had any cardiac events in the 3-year period after their basic course of treatment with EDTA. Patients were not excluded because of severity of illness or for their refusal to stop smoking.

A good number of variables were present in the study population, some of which are discussed in the subsection titled Patient Population. Many patients continued to receive intravenous EDTA treatments throughout the 3-year follow-up period. Others had no follow-up treatments. Conventional medical treatment including medications was continued as indicated for the patients in the study. Most patients continued to be followed by their cardiologists or other conventional physicians.

Outcome Measures

The primary outcome measures were the occurrence of an MI or stroke (defined as a 'cardiac event') and death from any cause during the 3-year follow-up period. The occurrence of these events was determined from the patient chart and from telephone calls to patients from the technician who completed the data forms.

A secondary outcome measure was whether the patient had CABG or angioplasty (with or without stent placement) during the 3-year follow-up period. In accordance with usual practice, we also refer to these surgical procedures as 'cardiac events'. We acknowledge that these were elective events, probably but not necessarily performed because of a distinct worsening of symptoms. Cardiologists might have recommended these procedures on the basis of insufficient improvement of findings that were present prior to treatment with EDTA.

As another secondary outcome measure, we determined from the chart and confirmed by patient telephone interview whether the patient had vascular symptoms at the beginning and at the end of EDTA treatment. These symptoms included chest pain, shortness of breath, dizziness, memory loss, cold extremities and leg pain while walking. It was further determined whether the symptoms were better, worse or the same at the 3-year follow-up. No attempt was made to quantify the specificity or the severity of the symptoms.

From the eight centres, a total of 248 patients passed the initial screening and were assigned identification numbers. Upon careful review of each patient's chart, we found that five did not actually meet the inclusion criteria, one was a duplicate and three had not given adequate informed consent. All of these patients were excluded. There were incomplete data on 19 patients, although all of these patients did have adequate data on the primary and secondary outcomes (only one of these 19 patients had a cardiac event after treatment with EDTA, namely CABG). Two hundred and twenty patients had a complete database for the study. Only those 220 patients were included in the final analysis. We found no evidence of patients discontinuing treatment because of adverse events or the incidence of a cardiac event.

Statistical Analysis

Longitudinal data analyses were used to evaluate the effect of chelation therapy on the rates of primary and secondary endpoints for patients with vascular diseases. We focused on the change of cardiac event rates during 3-years follow up from the baseline levels. The method of generalised estimating equations[13,14] was used for the binary repeated measures analysis. The associations between the rates for endpoints with risk factors such as age, body mass index and smoking status were also obtained through generalised estimating equations' models.

Since there was no separate control group in this retrospective study, we looked at other databases in the literature with similar patient characteristics in order to ascertain rates of subsequent cardiac events experienced in those patient populations. We searched PubMed using the terms 'percutaneous transluminal coronary angioplasty' (PTCA) and 'coronary artery bypass surgery'. The searches identified seven randomised trials[15-21] comparing PTCA, CABG and medical treatments, which had a similar follow-up period to our chelation study and covered the same approximate time period. These patient populations were carefully scrutinised to be sure that they were comparable with the patients in our study. The endpoints were essentially the same as in our study except that they did not include stroke as an event. We then compared the incidence of cardiac events for the patients treated with EDTA chelation therapy with the studies of those patients treated initially with PTCA, CABG and conventional medical

Table I. Number and percentage of patients with the primary endpoints at baseline vs 3-year follow-up

Primary endpoint	Baseline			3-year follow-up			p-Value
	n	patients with primary endpoints		n	patients with primary endpoints		
		no.	%		no.	%	
Myocardial infarction	220	38	17.3	220	0	0	NA
Stroke	220	15	6.8	220	4	1.8	0.02
Death	NA	NA	NA	220	0	0	NA

n = number of patients in study; **NA** = not applicable.

therapy. We performed a meta-analysis with WinBUGS software (http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml) using Bayesian hierarchical models.

Results

Primary and Secondary Endpoints

MI, stroke and death were the primary endpoints. At the beginning of EDTA therapy, there were 38 (17.3%) patients showing a previous history of MI and 15 (6.8%) showing a history of stroke. During the 3-year follow-up period in this high-risk population of 220 patients with known vascular disease, there were no MIs, none of the patients died and there were only four strokes. All of the four patients with strokes recovered completely. The incidence of the primary endpoints is shown in table I.

For secondary endpoints, there were six CABG procedures and two angioplasties during the follow-up period. One hundred and eighty-five patients with vascular symptoms began treatment. Of those, 127 patients (68.7%) had no symptoms at the end of 3 years. Fifty-eight (31.3%) patients of the symptomatic group continued to have symptoms after 3 years. Of the 35 patients from whom a lack of symptoms were recorded at the beginning of treatment, three had developed symptoms at the end of 3 years and 32 continued symptom-free. Of the patients with symptom documentation, 84.1% had symptoms at the beginning of EDTA therapy and 27.7% had symptoms at the end of 3 years of follow-up. There was no correlation between the number of treatments and resolution of symptoms. These data are summarised in table II.

Patient Population

Of the patients, 72.3% were male and 27.7% female. The average age of the patient population at the beginning of treatment was 64 years. The mean patient height was 170cm (67 inches) and mean weight was 80kg (177 pounds). At the beginning of EDTA treatment, 18.2% of patients smoked and at the end of the 3-year follow-up the rate was 8.2%. More than 90% of the patients were aware at the beginning of treatment of diet and exercise guidelines for patients with vascular problems, and no detailed education or behaviour modification programme was initiated.

At the initiation of treatment, 17.3% of the patients gave a history of previous MI, 20.5% CABG, 11.8% angioplasty, 6.8% stroke, 5.9% transient ischaemic attack and 0.9% endarterectomy. Of the 185 patients with symptoms, 37.5% had been told that they should undergo CABG or angioplasty, and they chose to receive EDTA chelation therapy instead. Of the remaining patients with symptoms, 8.2% had been told that they needed vascular surgery but that it was not possible because they were too high risk.

The total number of treatments for each patient was at least 20. Most patients received a basic course of 30 treatments and continued with maintenance treatments every month or two. The average number of treatments per patient in the 3-year period was 58.

Table II. Number and percentage of patients with the secondary endpoints at baseline vs 3-year follow-up

Secondary endpoint	Baseline			3-year follow-up			p-Value
	n	patients with secondary endpoints		n	patients with secondary endpoints		
		no.	%		no.	%	
Symptoms	220	185	84.1	220	61	27.7	<0.0001
Coronary artery bypass surgery	220	45	20.5	220	6	2.7	<0.0001
Angioplasty	220	26	11.8	220	2	0.9	0.0002
Transient ischaemic attack	220	13	5.9	220	1	0.5	0.01
Endarterectomy	220	2	0.9	220	1	0.5	0.57

n = number of patients in study.

Table III. Baseline characteristics of the randomised controlled trials

Study	Group[a]	n	Follow-up (mo)	Age (y)	Male (%)	Nonsmoker (%)	Vessel involved
AVERT[17]	PTCA	177	18	NP	NP	NP	Single and multi-vessels
	Medical therapy	164	18	NP	NP	NP	Single and multi-vessels
Folland et al.[15]	PTCA	51	60	NP	100.00	NP	Double vessel
	Medical therapy	50	60	NP	100.00	NP	Double vessel
RITA-2[16]	PTCA	504	32	58 (<50 to >70)	81.55	NP	Single and multi-vessels
	Medical therapy	514	32	58 (<50 to >70)	82.49	NP	Single and multi-vessels
MASS[19]	CABG	70	36	58 (47–69)	82.86	47.14	Single vessel
	PTCA	72	36	54 (45–63)	80.56	50.00	Single vessel
	Medical therapy	72	36	58 (51–65)	81.94	50.00	Single vessel
EAST[18]	CABG	194	36	62	74.00	NP	Multi-vessel
	PTCA	198	36	62	74.00	NP	Multi-vessel
Lausanne[20]	CABG	66	30	54 (52–57)	80.00	21.21	Single vessel
	PTCA	68	30	57 (54–60)	80.00	13.24	Single vessel
RITA[21]	CABG	501	30	57 (<40–79)	78.64	NP	Single and multi-vessels
	PTCA	510	30	57 (<40–79)	82.75	NP	Single and multi-vessels
Chelation	Chelation	220	36	64 (40–85)	71.00	47.80	Single and multi-vessels

a Medical therapy refers to conventional medical therapy.

AVERT = Atorvastatin Versus Revascularization Treatments; **CABG** = coronary artery bypass surgery; **EAST** = Emory Angioplasty versus Surgery Trial; **MASS** = Medicine, Angioplasty or Surgery Study; **n** = number of patients; **NP** = not reported in the article; **RITA** = Randomized Intervention Treatment of Angina; **RITA-2** = second Randomized Intervention Treatment of Angina; **PTCA** = percutaneous transluminal coronary angioplasty.

A number of variables related to patients were analysed to determine if they were associated with improvement in symptoms. Age, weight and total number of treatments were not found to be significant factors. Some patients were treated with a 50 mg/kg dose adjusted for creatinine clearance, up to a maximum of 3g of EDTA in 500 cm^3 of solution. Others received a maximum of 1.5g in 250 cm^3 of carrier solution. Both doses are allowed in the published protocol.[4] No advantage was detected for the higher dose. Slightly more males than females had improved symptoms. The severity of the disease did not correlate with the likelihood of symptom resolution with treatment. Those who chose to rely on chelation therapy despite being told to consider CABG improved equally well as those who were not advised to have surgery. As expected, those who continued to smoke during the treatment period were less likely to improve their symptoms than the non-smokers. Those who quit smoking during the treatment period did not have better symptomatic improvement than the smokers who did not quit. A majority of the patients who continued to smoke did report improvements in their symptoms.

Comparable Trials

The comparable trials we identified contained 15 groups of patients with single- and multi-vessel disease with follow-up data on cardiac events after conventional medical and/or surgical treatment. Seven groups with a total of 1580 patients were treated primarily with angioplasty (PTCA). Five groups with a total of 1345 patients were treated primarily with CABG. The surgical groups also received medical therapy. Three groups with 284 patients were treated only with conventional medical therapy.

The similarity of patient populations between our study and the comparable studies we identified is shown in table III. Average age for the chelation group was 64 years, and in the other trials it was 58 years. In the chelation group, 72% were males, whereas 82% were males in the other trials. Of the chelation group, 48% had never smoked, compared with 42% of the participants in the other trials. The follow-up monitoring period was 36 months for the chelation group and an average of 34 months for the controlled trials. The number of patients in the chelation group was 220, and there was a total of 3209 patients in the other trials, which computes to an average of 214 patients per group.

In the pooled population of the comparable published studies, 42% were treated initially with CABG, 49% with PTCA and 9%

with only conventional medical therapy. In the chelation group, 45.7% of the symptomatic patients were told they needed CABG, and they either refused or were not given surgery because the level of risk was considered to outweigh the potential benefit. We concluded that the identified groups were indeed comparable with our study group and there were no reasons to believe that the various treatment groups were significantly different from each other.

The primary endpoints in our study were MI, stroke and death from any cause. None of the 220 patients in the chelation group had an MI (0%), with a 95% upper confidence bound of 1.3% during the 3-year follow-up period. In the comparable groups, 7.3% of those treated initially with PTCA, 7.8% of those treated with CABG and 3.6% of those treated with conventional medical therapy had an MI. Combining all of the standard therapies, the incidence of MI in a 3-year follow-up was 6.8% (95% CI 4.7, 9.6). If the 220 patients in our treatment group had been treated only with conventional therapies, we would have expected that 15 of them would have suffered an MI. Remarkably, none of the patients treated with EDTA chelation therapy had an MI during the 3-year follow-up after beginning treatment.

Likewise, none of the chelation group died from any cause during the 3-year follow-up. The incidence of death was 3.2% with PTCA, 4.0% with CABG and 1.3% with conventional medical therapy. The composite death rate with standard therapies was 2.8% in a 3-year follow-up (95% CI 2.0, 3.6). Thus, for 220 patients treated only with conventional therapies, we would have expected six deaths. In our actual EDTA treatment group, there were no deaths during the follow-up period.

Four of the chelation group patients had strokes during the follow-up period. The incidence of strokes was not documented in the published clinical trials with conventional therapies. However, all of the four patients who suffered strokes had full recovery.

Secondary endpoints in our study included the need for PTCA and the need for CABG during the follow-up period. Only 0.9% of those treated initially with chelation required a subsequent PTCA. Of those in the compared studies, 22.3% of those treated initially with PTCA needed another one, 5.5% of those treated primarily with CABG subsequently needed a PTCA and 15.5% of those treated with conventional medical therapy had a PTCA in the follow-up period. The overall incidence of the need for PTCA during the follow-up period was 14.1% (95% CI 9.4, 20.5). For our group of 220 patients, the meta-analysis predicted that 31 PTCAs would have been needed. The actual incidence was only two PTCAs. This is a 93.6% reduction in the need for a PTCA for patients treated with chelation therapy in the study group.

The chelation group had a follow-up incidence of need for a CABG of 2.7%. The need for CABG was 11.8% in the PTCA group, 1.2% in the CABG group and 4.4% in the conventional medical therapy group. The overall incidence of the need for CABG with conventional therapies was 7.4% in the 3-year follow-up. The predicted number of new CABGs required for the 220 patients in our treatment group was 16. Only six CABG procedures were actually required in the EDTA treatment group. This is a 62.5% reduction for the need for CABG in those patients treated with chelation therapy as compared with conventional therapies. These findings are summarised in table IV and figure 1.

Comment

The rates of cardiac events in these high-risk patients treated with EDTA chelation therapy were much lower than for those who were treated only with conventional medical and surgical therapy. In particular, there were no deaths, no MIs and four minor strokes during a 3-year follow-up period in this group of 220 patients treated with chelation therapy. Since heart attacks and strokes continue to be two of the three major causes of death, it is obvious that current therapies and prevention techniques are inadequate. Innovative therapies such as chelation therapy have been dismissed in the past without sufficient scientific investigation. This study appears to indicate that chelation therapy might well be an effective secondary prevention tool to reduce mortality and morbidity for patients with known vascular disease. The incidences of subsequent MI and death from any cause appear to be lower utilising chelation therapy than relying on just PTCA, CABG and/or conventional medical therapy.

There were several strokes in the chelation group, but a comparable study group was not identified. Of note was that all of the four patients who suffered a stroke during the follow-up period had an excellent recovery from their stroke. It is possible that treatment with EDTA might have lessened the severity of the strokes, even though they did occur. We postulate that one potential mechanism for this result could be the anticoagulant effect of EDTA.

Table IV. Predicted cardiac events (based on meta-analysis) and actual events in the 220-patient study group

Cardiac event	Predicted number of events with conventional medical and surgical therapy	Observed number of events with chelation therapy	Reduction (%)
MI	15	0	100
Death	6	0	100
CABG	16	6	62.5
PTCA	31	2	93.6

CABG = coronary artery bypass surgery; **MI** = myocardial infarction; **PTCA** = percutaneous transluminal coronary angioplasty.

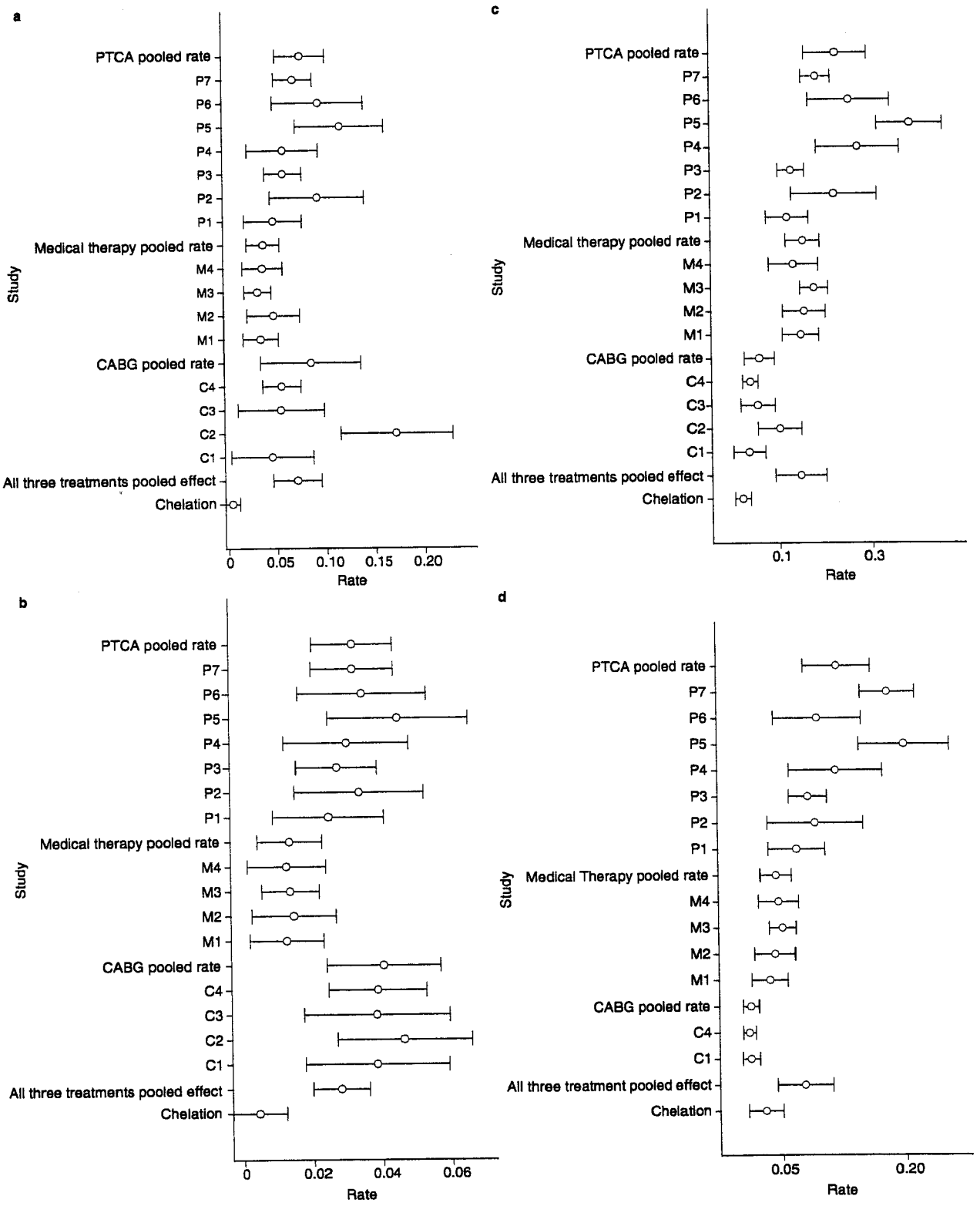

Fig. 1. Endpoints and study trials by type of treatment: (**a**) myocardial infarction, (**b**) death, (**c**) need for percutaneous transluminal coronary angioplasty (PTCA) and (**d**) need for coronary artery bypass surgery (CABG). **C** = CABG; **M** = medical therapy; **P** = PTCA. Study codes: **1** = AVERT (Atorvastatin Versus Revascularization Treatments)[17]; **2** = Folland et al.[15]; **3** = RITA-2 (second Randomized Intervention Treatment of Angina)[16]; **4** = MASS (Medicine, Angioplasty or Surgery Study)[19]; **5** = EAST (Emory Angioplasty versus Surgery Trial)[18]; **6** = Lausanne[20]; **7** = RITA (Randomized Intervention Treatment of Angina)[21].

According to our comparison by meta-analysis, the need for further surgical intervention was much less in the group treated with EDTA. The group treated with chelation therapy had a 93.6% reduction in the need for PTCA over the groups identified from the medical literature that were treated with conventional therapies. The chelation group had a 62.5% reduction in the need for CABG surgery compared with the groups treated with conventional therapies.

In recent years, the simultaneous use of lifestyle changes, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, antiplatelet agents, folic acid and aggressive lipid lowering measures has been employed more commonly. The addition of chelation therapy to this regimen might further reduce cardiac events for patients at risk. Another obvious goal is to move toward the elimination of the need for surgical procedures altogether, which would greatly reduce morbidity, mortality and healthcare costs. Our study indicates that the widespread use of chelation therapy would likely be effective in reducing the need for surgical interventions.

Most patients with vascular symptoms treated with EDTA can apparently expect an improvement in symptoms. In fact, many appear to become symptom-free. The possibility of an improved quality of life for symptomatic patients might alone be a reasonable basis for certain patients to choose to undergo the therapy now, even before definitive proof is available.

Possible mechanisms of action of EDTA to prevent cardiac and stroke events were discussed by Cranton and Frackelton.[22] They emphasised the reduction of free radicals and the antioxidant activity of removing heavy metals, iron and copper. Gutteridge[23] and Zylke[24] also noted the activity of EDTA in controlling oxygen radicals. Kindness and Frackelton[25] showed the beneficial effect of EDTA chelation on platelet aggregation and on the partial thromboplastin time. The most thorough discussions of possible mechanisms of action are contained in Cranton's textbook[4] and in Olmstead's monograph.[5]

Treatment with intravenous EDTA according to the published protocol, which is what was used in this study, appears to be safe. This confirms previous observations and studies.[26,27] There were no significant complications reported for the 220 patients in this study. The results of our study, coupled with the work of Lin et al.[2] showing improvement in kidney function for patients with mild to moderate renal disease, should reassure critics[28] who have expressed concerns that the therapy might adversely affect kidney function. Kidneys are apparently at risk only if the treatments are given too fast or at too high a dose. When properly administered, intravenous EDTA appears to be very safe.

Although the patients in this study generally were encouraged to continue conventional medical care, a number of them were motivated to reduce the need for medications because of a concern for adverse effects. Since many of them no longer had symptoms at the end of the basic course of treatment, we presume that the number of medications required was successfully reduced, although this was not documented in our study. Although cost factors were not quantified, it appeared that the cost of chelation therapy reduced the total cost of treatment. By avoiding additional drugs and surgery, patients treated with chelation therapy probably incurred less medical expense.

Conclusion

We conclude that the data from this study indicate that the number of subsequent cardiac events in patients at risk because of their known vascular disease might be reduced by the use of EDTA chelation therapy. Patients who received EDTA treatment had substantially fewer MIs and deaths than our comparison groups during the 3-year follow-up period. Patients from the comparison groups who received primary treatment with CABG, PTCA (with or without stents) or just conventional medical therapy required many more cardiac surgical procedures than those who received EDTA chelation therapy. Chelated patients continued to receive conventional medical therapy as well, although they were less likely to be followed closely by a cardiologist. We suggest that the best treatment and prevention programme might be to include EDTA chelation therapy along with conventional medical therapy as a primary treatment, reserving CABG and PTCA with stent placements only for cases in which the need is obvious and urgent. Of course, randomised controlled trials sufficiently large for statistical significance and with meaningful endpoints are still needed.

Randomised controlled trials that have been performed to date on EDTA chelation therapy have been too small for definitive conclusions. They have not shown major improvements in testing parameters. However, when the more important endpoints of cardiac and stroke events and premature deaths are examined, as was done in this study, the therapy appears to be quite effective. In addition, symptomatic improvement was experienced by a large percentage of patients in this study, which is consistent with the considerable body of uncontrolled scientific literature that is available.[4,5]

Patients at least in part served as their own controls for this study. In addition, comparable groups were identified from the medical literature, and a meta-analysis was performed to further assess the impact of treatment with EDTA chelation therapy. We acknowledge that the compared groups were from randomised controlled trials and that our group was not. This might be considered a weakness in the study. However, a thorough analysis of the

subjects in the compared groups indicates that our observation group was very similar to the groups from the literature, especially in terms of degree of cardiac risk. Further, by examining indisputable endpoints such as cardiac events, we feel that the comparison was indeed valid. It appears from our study that EDTA chelation therapy improves outcomes for patients with documented vascular disease, in particular those with coronary artery disease.

The much larger TACT study, which is a randomised, controlled clinical trial with at least 3 years of follow-up, is currently in progress.[12] This trial will provide more definitive evidence on this controversial therapy that continues to be used by a minority of practitioners in many countries throughout the world. Although there is still insufficient evidence to recommend chelation therapy as a standard therapy for secondary prevention at this time, there is certainly a reasonable basis and sufficient safety data for knowledgeable practitioners to utilise the therapy on an off-label basis with informed consent in selected cases. Patients for whom surgical intervention is not an option because of high risk might be particularly good candidates for the therapy.

Acknowledgements

The authors wish to thank the following people who made major contributions to the gathering and organising of data for this project: Elizabeth Angus, Larry Mervine, Lisa Wellinghoff and Luo Junxiang.

The statistical analysis was performed by Rakesh Shukla, Professor of Biostatistics and Director of the Center for Biostatistical Services at the University of Cincinnati Medical Center.

We are grateful for financial support from the following organisations: American Institute of Medical Preventics, Frederick S. Upton Foundation, National Heart Council, Health Research Foundation, Foundation for Research and Development of Complementary and Alternative Medicine, Gordon Research Institute, Trillium Health Center, Magnetico, Haelen Products, Apothecure Pharmacy, Douglas Labs and Longevity Plus.

None of the authors has any financial interest in companies that produce and sell EDTA, nor any potential conflicts of interest that are directly relevant to the contents of this manuscript.

References

1. Lamas GA, Ackerman A. Clinical evaluation of chelation therapy; is there any wheat amidst the chaff? Am Heart J 2000; 140: 4-5
2. Lin J-L, Lin-Tan D-T, Hsu K-H, et al. Environmental lead exposure and progression of renal diseases in-patients without diabetes. N Engl J Med 2003; 348: 277-86
3. Nash D, Magder L, Lustberg M, et al. Blood lead, blood pressure, and hypertension in perimenopausal and post menopausal women. JAMA 2003; 289: 1523-32
4. Cranton EM. A textbook on EDTA chelation therapy. 2nd ed. Charlottesville (VA): Hampton Roads, 2001
5. Olmstead SF. A critical review of EDTA chelation therapy in the treatment of occlusive vascular disease. Klamath Falls (OR): Merle West Medical Center Foundation, 1998
6. Chappell LT, Stahl JP. The correlation between EDTA chelation therapy and improvement in cardiovascular function: a meta-analysis. J Adv Med 1993; 6: 139-63
7. Hancke C, Flytlie K. Benefits of EDTA chelation therapy in arteriosclerosis: a retrospective study of 470 patients. J Adv Med 1993; 6: 161-71
8. Hancke C. The long-term effect of chelation therapy: a 6-12 year follow-up of a 1993 study. Clin Pract Altern Med 2000; 1: 158-63
9. Guldager B, Jelnes R, Jorgensen SJ, et al. EDTA treatment of intermittent claudication: a double-blind, placebo controlled study. J Intern Med 1992; 231: 261-7
10. van Rij AM, Soloman C, Packer SGK, et al. Chelation therapy for intermittent claudication: a double-blind, randomized controlled trial. Circulation 1994; 90: 1194-9
11. Knudtsen ML, Wyse DG, Gailbraith PD, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. JAMA 2002; 287: 481-6
12. National Institutes of Health. NIH launches large clinical trial on EDTA chelation therapy for coronary artery disease [online]. Available from URL: http://nccam.nih.gov/chelation/pressrelease.htm [Accessed 2005 Jul 28]
13. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986; 42: 121-30
14. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986; 73: 13-22
15. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a veterans affairs cooperative randomized trial. Veterans affairs ACME investigators. J Am Coll Cardiol 1997; 29: 1505-11
16. Coronary angioplasty versus medical therapy for angina: the second Randomized Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. Lancet 1997; 350: 461-8
17. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease: Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med 1999; 341: 70-6
18. King SB, Lembo NJ, Kosinski AS, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery: Emory Angioplasty versus Surgery Trial (EAST). N Engl J Med 1994; 331: 1044-50
19. Hueb W, Arie S, Oliveira SA, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective randomized trial for single proximal left anterior descending artery stenoses. J Am Coll Cardiol 1995; 26: 1600-5
20. Goy J-J, Eeckhout E, Burnand B, et al. Coronary angioplasty versus left internal mammary grafting for isolated proximal left anterior descending artery stenosis. Lancet 1994; 343: 1449-53
21. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet 1993; 341: 573-80
22. Cranton EM, Frackelton JP. Free radical pathology on age-associated diseases; treatment with EDTA chelation nutrition and antioxidants. J Holist Med 1984; 6: 6-37
23. Gutteridge JMC. Ferrous-salt-promoted damage to deoxyribose and benzoate, the increased effectiveness of hydroxy-radical scavengers in the presence of EDTA. Biochem J 1987; 243: 709-14
24. Zylke J. Studying oxygen's life-and-death roles if taken from or reintroduced into tissue. JAMA 1988; 259: 964-5
25. Kindness G, Frackelton JP. Effect of ethylene diamine tetraacetic acid (EDTA) on platelet aggregation in human blood. J Adv Med 1989; 2: 519-30
26. Cranton EM. Kidney effects of ethylene diamine tetraacetic acid (EDTA): a literature review. J Holist Med 1982; 4: 152-7
27. McDonagh EW, Rudolph CJ, Cheraskin E. The effect of EDTA chelation therapy plus supportive multivitamin-trace mineral supplementation upon renal function: a study in serum creatinine. J Adv Med 1989; 2: 235-44
28. Oliver LD, Mehta R, Sarles HE. Acute renal failure following administration of ethylenediamine-tetraacetic acid (EDTA). Tex Med 1984; 80: 40-2

Correspondence and offprints: Dr *L. Terry Chappell*, PO Box 248, Bluffton, OH 45817, USA.
E-mail: Chappell@wcoil.com