The Trial to Assess Chelation Therapy - TACT

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References

Description:

Chelation therapy with disodium ethylene diamine tetra acetic acid (EDTA) is sometimes suggested as an alternative medicine approach to the treatment of coronary artery disease (CAD). However, there are limited data to support its use. The current trial sought to compare outcomes with EDTA versus placebo infusion in post-myocardial infarction (MI) patients treated with medical therapy.

Hypothesis:

Chelation therapy with EDTA and high-dose vitamin therapy both would be superior to placebo in post-MI patients.

Study Design

- Randomized
- Blinded
- Parallel

- Factorial

Patient Populations:

- Age 50 or older
- MI >6 months prior
- Creatinine <2.0 mg/dl
- No coronary or carotid revascularization within 6 months
- No active heart failure or heart failure hospitalization within 6 months
- Able to tolerate 500 cc infusions weekly
- No cigarette smoking within 3 months

Number of enrollees: 1,708
Median duration of follow-up: 55 months
Median patient age: 65 years
Percentage female: 18%

Primary Endpoints:

- Death, MI, stroke, coronary revascularization, hospitalization for angina

Drug/Procedures Used:

In a 2 x 2 factorial design, patients were randomized to receive either chelation or placebo infusions, and oral vitamins or placebo.

Chelation vs. placebo: A total of 40 chelation or matching placebo infusions were administered (at least 3 hours for each infusion). These included 30 weekly infusions followed by 10 maintenance infusions 2-8 weeks apart. The chelation infusion consisted of disodium EDTA, 3 grams, adjusted downward based on estimated glomerular filtration rate, ascorbic acid (7 grams), magnesium chloride (2 grams), potassium chloride (2 mEq), sodium bicarbonate (840 mg), pantothenic acid, thiamine, pyridoxine, procaine (100 mg), unfractionated heparin, 2500 U, and sterile water to 500 ml. Placebo infusion consisted of 500 ml of normal saline with 1.2% dextrose.

Vitamin vs. placebo: Three caplets of multivitamins twice daily were administered. The active high-dose vitamin treatment was a 28 component mixture.

Concomitant Medications:

Statins (73%), aspirin (83%), beta-blockers (72%).

Principal Findings:

A total of 1,708 patients were randomized, 839 to chelation and 869 to placebo, and 853 to high-dose vitamins and 855 to placebo. Baseline characteristics were fairly similar between the two arms. The majority of patients were Caucasian (90%), with diabetes in 31% and prior revascularization in 83%. The baseline low-density lipoprotein cholesterol was 89 mg/dl. About two thirds of patients completed all infusions, and three quarters completed at least 30. Approximately 17% withdrew consent.

Chelation therapy vs. placebo: The primary composite outcome of death, MI, stroke, coronary revascularization, and hospitalization for angina at 5 years was significantly lower in the chelation therapy arm as compared with the placebo arm (26.5% vs. 30%; hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.69-0.99, p = 0.035). This was driven predominantly by a reduction in the requirement for coronary revascularization (15.5% vs. 18.1%, p = 0.076). Other endpoints including mortality (10.4% vs. 10.7%, p = 0.64), MI (6.2% vs. 7.7%, p = 0.17), stroke (1.2% vs. 1.5%, p = 0.53), and angina hospitalization (1.5% vs. 2.1%, p = 0.36) were similar between the two arms. There appeared to be significant effect modification for the primary endpoint by MI location (p = 0.03), angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker at baseline (p = 0.04), and diabetes (p = 0.02). Diabetic patients in particular seemed to derive a higher benefit with chelation therapy as compared with placebo (HR 0.61, 95% CI 0.45-0.83, p = 0.002). No difference was noted in nondiabetics (p = 0.73).

Quality-of-life measures, as assessed by changes in Duke Activity Status Index, Short Form-36 Mental Health Inventory-5, and the Seattle Angina Questionnaire, were similar between the two arms over 24 months of follow-up.

Adverse events were mostly similar, although hypocalcemia (6.2% vs. 3.5%, p = 0.008) was higher in the chelation therapy arm.

High-dose vitamins vs. placebo: The primary composite outcome of death, MI, stroke, coronary revascularization, and hospitalization for angina at 5 years was similar between the vitamin and placebo arms (34.2% vs. 37%; HR 0.89, 95% CI 0.75-1.07, p = 0.21). Individual endpoints including mortality (10% vs. 11%, p = 0.61), MI (7% vs. 7%, p = 0.79), stroke (1% vs. 2%, p = 0.14), coronary revascularization (15% vs. 18%, p = 0.13), and angina hospitalization (1% vs. 2%, p

= 0.36) were similar between the two arms. Rate of discontinuation in the vitamin arm was very high (50%).

Chelation/high-dose vitamins vs. placebo/placebo: On subgroup analysis, the primary endpoint was significantly reduced in patients receiving chelation therapy + high-dose vitamins compared with placebo for both treatments (26% vs. 32%, p = 0.016). Cardiovascular death/MI/stroke was similarly reduced (p = 0.046), as was coronary revascularization (p = 0.017).

Diabetes subset (n = 633): For chelation therapy versus placebo, the primary composite outcome of death, MI, stroke, coronary revascularization, and hospitalization for angina at 5 years was significantly lower in the chelation therapy arm as compared with the placebo arm (HR 0.59, 95% CI 0.44-0.79, p = 0.0002). Other endpoints including mortality (p = 0.01), recurrent MI (p = 0.015), and coronary revascularizations (p = 0.042) were lower in the chelation therapy arm.

Interpretation:

The results of the TACT trial indicate that a 10-component disodium EDTA chelation and ascorbate regimen was superior to placebo in post-MI patients who were also on a good medical regimen. The majority of this benefit was by reduction in the need for coronary revascularizations. On the other hand, high-dose vitamins were not beneficial in this patient population. Interestingly, patients receiving chelation therapy demonstrated no difference in quality-of-life outcomes.

Chelation therapy for the treatment of CAD has been a controversial topic. The results of this trial are surprising since all prior studies on this topic have been negative. It is possible that the benefit noted in this trial is due to other healthy lifestyle practices promoted with chelation therapy such as smoking cessation, weight loss, eating more fruits and vegetables, avoiding foods high in saturated fats, and regular exercise. There was also a high concentration of antioxidants in the chelation infusion mixture.

Future studies will need to replicate these hypothesis-generating findings and also determine possible mechanisms of action. Chelation therapies are also very expensive in general, and future studies will also need to determine cost-effectiveness. The high rate of withdrawal of consent makes interpretation of this trial challenging.

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Chelation + high-dose vitamins vs. placebo: Presented by Dr. Gervasio Lamas at the American Heart Association Scientific Sessions, Dallas, TX, November 20, 2013.

Diabetes subset: Presented by Drs. Esteban Escolar and Gervasio Lamas at the American Heart Association Scientific Sessions, Dallas, TX, November 19, 2013.

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