Chelation therapy may result in small reduction of risk of CV events

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Although chelation therapy with the drug disodium EDTA has been used for many years with limited evidence of efficacy for the treatment of coronary disease, a randomized trial that included patients with a prior heart attack found that use of a chelation regimen modestly reduced the risk of a composite of adverse cardiovascular outcomes, but the findings do not support the routine use of chelation therapy for treatment of patients who have had a heart attack, according to a study in the March 27 issue of *JAMA*.

Chelation therapy is an intravenous administration of chelating agents (such as disodium ethylene diamine tetraacetic acid [EDTA]) to treat heavy metal toxicity. Based on favorable anecdotal and case report experience, chelation therapy has evolved in recent decades to include treatment for coronary and peripheral artery disease. "Three small clinical trials have assessed the effects of chelation on surrogate outcomes, such as walking distance in patients with claudication and time to exercise-induced ischemia in patients with coronary disease. These studies did not find any evidence of treatment efficacy but were underpowered for evaluation of clinical events," according to background information in the article.

"As a consequence, mainstream medical organizations consider the therapeutic value of chelation for atherosclerotic vascular disease unproven and the use of this therapy potentially dangerous. Disodium EDTA, particularly when infused too rapidly, may cause hypocalcemia [abnormally low level of calcium in the blood] and death," the authors

write. Chelation therapy with disodium EDTA has been used for more than 50 years to treat atherosclerosis.

Gervasio A. Lamas, M.D., of the Columbia University Division of Cardiology at Mount Sinai Medical Center, Miami Beach, Fla., and colleagues conducted the Trial to Assess Chelation Therapy (TACT) to determine if an EDTA-based chelation regimen reduces cardiovascular events. The randomized trial enrolled 1,708 patients 50 years of age or older who had experienced a myocardial infarction (MI; heart attack) at least 6 weeks prior. Participants were recruited at 134 U.S. and Canadian sites. Enrollment began in September 2003 and follow-up took place until October 2011. Two hundred eighty-nine patients (17 percent of total; n=115 in the EDTA group and n=174 in the placebo group) withdrew consent during the trial. The median (midpoint) age was 65 years. The primary end point for the trial was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. Qualifying previous heart attacks occurred a median of 4.6 years before enrollment.

Patients were randomized to receive 40 infusions of a 500-mL chelation solution (3 g of disodium EDTA, 7 g of ascorbate, B vitamins, electrolytes, procaine, and heparin) (n=839) vs. placebo (n=869) and an oral vitamin-mineral regimen vs. an oral placebo. Infusions were administered weekly for 30 weeks, followed by 10 infusions 2 to 8 weeks apart. Fifteen percent discontinued infusions (n=38 [16 percent] in the chelation group and n=41 [15 percent] in the placebo group) because of adverse events.

The researchers found that the primary end point occurred in 222 (26 percent) of the chelation group and 261 (30 percent) of the placebo group. "There was no effect on total mortality (chelation: 87 deaths [10 percent]; placebo, 93 deaths [11 percent]), but the study was not powered for this comparison. The effect of EDTA chelation on the

components of the primary end point other than death was of similar magnitude as its overall effect (MI: chelation, 6 percent; placebo, 8 percent; stroke: chelation, 1.2 percent; placebo, 1.5 percent; coronary revascularization: chelation, 15 percent; placebo, 18 percent; hospitalization for angina: chelation, 1.6 percent; placebo, 2.1 percent)."

Revascularizations accounted for 45 percent of the primary end point events. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 96 chelation patients (11 percent) and 113 placebo patients (13 percent).

The authors note that the study had several limitations, including an unusually high number of patients withdrawing consent.

"In stable patients with a history of MI, the use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of a composite of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI," the authors conclude.

In an accompanying editorial, Howard Bauchner, M.D., Editor-in-Chief, *JAMA*, and colleagues discuss some of the concerns regarding the TACT trial and the factors involved in deciding to publish the study.

"Clinical decision making is complex, reflecting a synthesis of evidence, physician experience, and patient preference, bound together by societal norms. As such, very few studies should immediately change clinical practice but, rather, most add incremental knowledge to the complex puzzle of a clinical decision. However, based on full consideration of the strengths and limitations of TACT, the conclusion is clear and should influence practice—these findings do not support the routine use of

chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease. Whether chelation therapy may have any role in the prevention and treatment of cardiovascular disease remains to be determined."

Steven E. Nissen, M.D., of the Cleveland Clinic Foundation, writes in an accompanying editorial that "TACT represents a situation in which many important limitations in the design and execution of a clinical trial compromise the reliability of the study and render the results difficult to interpret."

"Nonetheless, all randomized controlled trials should be published because even failed trials provide valuable scientific lessons for the medical community. Accordingly, TACT provides useful insights into the overwhelming challenges faced when trying to determine the effectiveness of an unusual and controversial therapy."

"Given the numerous concerns with this expensive, federally funded clinical trial, including missing data, potential investigator or patient unmasking, use of subjective end points, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and do not demonstrate a benefit of chelation therapy. The findings of TACT should not be used as a justification for increased use of this controversial therapy."

More information: *JAMA*. 2013;309(12):1241-1250
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