Clinical Practice Guideline: **Intravenous Chelation Therapy**

Date of Implementation: **June 21, 2007**

Product: **Specialty**

GUIDELINES

American Specialty Health – Specialty (ASH) considers intravenous chelation therapy using EDTA (ethylene diamine tetra-acetic acid) for heavy metal toxicity medically necessary, and when used appropriately, its benefits may outweigh its risks.

ASH considers intravenous chelation therapy, used in a manner other than described above, not medically necessary and unproven because credible scientific evidence is inadequate to support the claimed applications of this procedure.

Patients must be informed verbally and in writing of the nature of any procedure or treatment technique that is considered experimental/investigational or unproven, poses a significant health and safety risk, and/or is scientifically implausible. If the patient decides to receive such services, they must sign a Member Billing Acknowledgment Form (for Medicare use Advance Beneficiary Notice of Non-Coverage form) indicating they understand they are assuming financial responsibility for any service-related fees. Further, the patient must sign an attestation indicating that they understand what is known and unknown about, and the possible risks associated with such techniques prior to receiving these services. All procedures, including those considered here, must be documented in the medical record. Finally, prior to using experimental/investigational or unproven procedures, those that pose a significant health and safety risk, and/or those considered scientifically implausible, it is incumbent on the practitioner to confirm that their professional liability insurance covers the use of these techniques or procedures in the event of an adverse outcome.

DESCRIPTION/BACKGROUND

Chelation therapy involves the administration of a chelating agent, either orally or intravenously, to remove undesirable substances from the blood. The most common chelating agent is ethylene diamine tetra-acetic acid (EDTA) which binds with heavy metals and allows their excretion through urination. The efficacy of chelation therapy is well established for heavy metal toxicity, particularly lead poisoning. However, some advocates claim this type of therapy is beneficial in treating conditions ranging from cardiovascular disease to autism.

In 1956, Clarke, et. al. reported improvements in symptoms and electrocardiogram findings in the majority of 20 patients with angina after infusions with EDTA. Even though there

was no evidence from well-designed trials, the use of EDTA to treat atherosclerotic disease continued for many years and yielded many reports of questionable clinical significance. In the 1970s chelation therapy had become a modality associated with complementary and alternative medicine.

EDTA chelation therapy is associated with an array of possible side effects including gastrointestinal complaints, diaphoresis, fever, leucopenia, kidney damage, mineral depletion, and hypocalcemia. There have been deaths associated with chelation therapy, particularly from hypocalcemia. Further, chelation therapy may produce nutritional deficiencies if patients are not adequately supplemented.

EVIDENCE REVIEW

Chelation therapy has a long-standing history of use for heavy metal toxicity and is currently used regularly to treat iron toxicity (Alymara et al. 2004, Cai et al. 2005, Franchini and Veneri 2004, Hershko et al. 2005a, Hershko et al. 2005b).

Chelation therapy as a treatment for cardiovascular disease has also been extensively studied. Olszewer and Carter (1988) present a retrospective case series of patients that underwent EDTA chelation therapy for chronic degenerative diseases including heart disease. The outcome measures in this paper are very poor but the authors suggest that a marked improvement was seen by patients that underwent this therapy. Due to serious methodological flaws, this paper is unable to tell us whether chelation therapy is effective.

Further review uncovered two randomized controlled trials of chelation therapy for cardiovascular disease. Chen et al. (2006) evaluated the effect of chelation therapy on blood pressure in children who had been exposed to lead. They found no association between blood pressure and chelation therapy as well as no association between blood pressure and lead levels in the children. Knudtson et al. (2002) evaluated the effect of EDTA chelation therapy on ischemic heart disease in a double blind randomized controlled trial. Both groups received vitamin therapy as well as cardiac rehabilitation; the only difference in the treatments between the control and treatment group was the EDTA chelating agents. They found that both groups showed modest improvements, but that there was no difference between the placebo and the treatment group, indicating that chelation therapy was not effective as a treatment for ischemic heart disease. While critics have argued that the vitamins given to the group are a part of chelation therapy and thus it cannot be claimed that chelation therapy does not work, the active element of chelation therapy is the chelating agents. Lamas et al. (2013) conducted a placebo-controlled, double-blind trial with 1,705 patients 50 years of age or older with a history of myocardial infarction at least six weeks prior. A series of forty chelation treatments with EDTA, ascorbate, B vitamins, electrolytes, procaine, and heparin vs. placebo was administered; and an oral vitamin/mineral regimen vs. oral placebo. The primary endpoint was total mortality, repeat MI, stroke, coronary revascularization procedures and hospitalizations. Result of the trial

showed a modest reduction of cardiovascular adverse outcomes with the chelation regimen compared with placebo. The authors recommended that this evidence would guide further research but was not sufficient to support routine use of chelation treatments for patients who have had MIs.

Lamas et al. (2014) conducted a double-blind, placebo-controlled, multicenter randomized trial of 1,708 post-myocardial infarction (MI) patients who received 40 EDTA chelation or placebo infusions plus 6 caplets daily of a 28-component multivitamin-multimineral mixture or placebo. The primary end points were total mortality, MI, stroke, coronary revascularization, or hospitalization for angina. In stable post-MI patients on evidence-based medical therapy, the combination of oral high-dose vitamins and chelation therapy compared with double placebo reduced clinically important cardiovascular events to an extent that was both statistically significant and of potential clinical relevance.

There have also been numerous systematic reviews evaluating chelation therapy for cardiovascular disease. Ernst (1997) evaluated chelation therapy for peripheral artery disease and Ernst (2000) evaluated chelation therapy for heart disease and found that there was no evidence that chelation therapy is any better than placebo. Seely et al. (2005) found that while there is a body of evidence to support chelation therapy for cardiovascular disease it is all poor quality, relying on uncontrolled trials and papers published in non-peer reviewed literature. They conclude that the high-quality evidence does not support chelation therapy. Shrihari et al. (2006) found that there was not enough data to support the use of chelation therapy for cardiovascular disease. Villarruz et al. (2002) presents a Cochrane Collaboration review on chelation therapy finds that there is insufficient evidence to support the use of chelation therapy for cardiovascular disease. The updated Cochrane review (2020) included five studies with nearly 2000 participants with conditions such as peripheral vascular disease or coronary artery disease. All studies compared EDTA to placebo. The studies generally didn't show a significant difference between the treatment and placebo groups and the evidence level was generally low. The authors concluded that there was still insufficient evidence to determine the effectiveness of chelation therapy for atherosclerotic disease.

Ibad et al. (2016) examined the effect of chelation therapy on cardiovascular diseases. Thirty-eight articles were reviewed including 20 case series and 7 randomized controlled trials. Sixteen case series and 3 randomized controlled trials showed benefit with chelation. The Trial to Assess Chelation Therapy (TACT) included 1,708 post-myocardial infarction patients and demonstrated benefit with chelation therapy, but TACT investigators concluded that their results did not support the routine use of chelation therapy for post-myocardial infarction patients. Authors concluded that the effectiveness of chelation therapy in reducing recurrent cardiovascular disease events is unclear, but possible, and warrants additional, carefully designed clinical trials.

Sultan et al. (2017) provided a narrative review highlighting the evidence from observational studies and RCTs in assessing the effect of chelation therapy on cardiovascular outcomes and potential for adverse effects or harm. The authors reported that although encouraging results were reported in TACT, the evidence is insufficient to recommend the routine use of chelation therapy even in the post-MI diabetic subgroup, which appeared to benefit. Unsubstantiated claims of chelation therapy as an effective treatment of atherosclerosis should be avoided and patients made aware of the inadequate evidence for efficacy and potential adverse effects, especially the harm that can occur if used as a substitute for proven therapies.

Ravalli et al. (2022) studied the effect of repeated EDTA on clinical outcomes in adults with cardiovascular disease. In this meta-analysis, 17 out of 24 studies showed improvement in outcomes after EDTA treatment. Outcomes measured were mortality, disease severity, plasma biomarkers of disease chronicity and quality of life. Benefit was larger in participants with diabetes and severe peripheral arterial disease. The authors offered that, "EDTA may eliminate toxic metals associated with atherosclerotic and oxidative vascular damage."

Some proponents claim chelation therapy can also treat autism and psycho-developmental disorders in children. A review of the literature located one study examining this topic. Dietrich et al. (2004) evaluated the effect of chelation therapy on the neuropsychological and behavioral development of lead exposed children in response to the theory that heavy metal toxicity is a cause of learning and developmental disorders such as autism. This randomized controlled trial found that chelation therapy is not associated with neuropsychological benefits in children with high heavy metal (lead) levels.

A study conducted by Wang et al. (2023) discusses how high levels of copper may affect cardiovascular risk. Cuproptosis is cell death related to high levels of copper. Copper promotes atherosclerotic plaque formation, increases inflammation, and worsens insulin resistance/diabetes risk. Copper chelating agents inhibit these effects and prevent atherosclerosis and acute inflammation reducing the risk of myocardial injury. Diseases with high levels of copper also demonstrate cardiac arrythmias from copper accumulation in the myocardium. Cuproptosis inhibitors may protect against atherosclerotic cardiovascular disease. Genes responsible for regulating copper levels may become dysfunctional allowing copper levels to rise, and disturbing mitochondrial enzyme function, and normal heart and blood vessel activity, as reported by Yang et al. (2023). This leads to cell death from high copper or cuproptosis. Therapies would include copper chelators to prevent cardiovascular diseases. Farrant et al. (2023) will be studying the effects of trientine, a selective copper chelator, on hypertrophic cardiomyopathy in a multicenter, double-blind randomized, placebo-controlled trial. Participants will receive chelation or placebo for 52 weeks. The primary outcome will be left ventricular mass

measured by cardiac MRI. Secondary outcomes will include exercise capacity, arrhythmias, and left ventricular function.

Pantane et al. (2023) discusses disruptions of iron homeostasis related to cardiovascular disease and ferroptosis. Iron accumulation in the myocardium results in cardiotoxicity and poor cardiac function. This dysfunction can be treated with iron chelators such as deferoxamine and deferiprone, and genetic regulation of ferroptosis. Nashwan and Yassin (2023) discusses iron overload that is common in patients with chronic kidney disease on dialysis and can lead to cardiovascular disease. While most iron chelators would be contraindicated for these patients, deferasirox, an oral iron chelator is a treatment option.

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