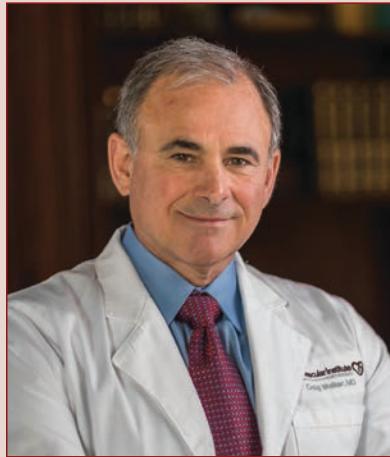


# Chelation Therapy: Is More Investigation Warranted?



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Hello and welcome to the October 2022 edition of *Vascular Disease Management*. As always there are multiple articles of interest in this month's publication. I have chosen to comment on Drs. Francisco Ujueta and Gervasio Lamas's article, "Is There a Role for Eddate Disodium Chelation in PAD and Specifically CLTI?"

I have chosen to comment on this article as there is an epidemic of critical limb-threatening ischemia (CLTI), and there were statistically significant improved outcomes in the Trial to Assess Chelation Therapy (TACT) in diabetic patients ( $P=.0002$ ) and in patients with self-identified peripheral arterial disease (PAD) ( $P=.0069$ ) with no difference compared with placebo of serious adverse events. The authors also reported limb salvage in an open-label trial of edetate disodium in 10 patients with CLTI who were deemed as having no other option for therapy. Seven of the 10 patients in the trial completed the course of 20 infusions. All of those who completed the 20-infusion treatment regimen avoided amputation and reported significant pain relief. The authors eloquently detail the history of chelation therapy with its successes and failures. The results of TACT are reported in detail. The authors discuss potential explanations as to the mechanisms of action that may have resulted in therapeutic benefit.

Newer interventional techniques, such as pedal loop reconstruction and direct venous arterialization, as well as pedal artery access, have redefined what represents a true "no option for revascularization" among patients presenting

with CLTI. Improved wound healing therapies show promise in improving outcomes. The Voyager and Compass trials have demonstrated improved outcomes in PAD patients via treatment with the factor Xa inhibitor rivaroxaban. There are newer diabetic and lipid management medications allowing clinicians to control risk factors more effectively. Despite these breakthroughs and improvements in present guideline directed therapies, major amputations remain common. Although many amputations are performed urgently as lifesaving procedures secondary to extensive tissue and bone damage or infection, most are secondary to inadequate revascularization of the ischemic limb. Unfortunately, and in my opinion inappropriately, some major amputations are still performed as primary treatment for CLTI without severe infection, without initial vascular assessment. We need more progress in treating ischemic limbs and preventing ischemia.

The TACT utilizing infusions of edetate disodium demonstrated significant benefit with chelation therapy in diabetic patients and patients with self-reported PAD. Interestingly, these results were achieved without the reduction of arterial calcium burden, which had initially been postulated as the presumed explanation of possible benefit with chelation. The small open-label trial in patients with nonhealing wounds is encouraging. Given these data, which are promising, more investigation of chelation therapy is warranted. In my opinion, it should be evaluated as primary therapy as well as in addition to improved revascularization techniques to treat individuals presenting with CLTI. One must also question if treatment with chelation therapy earlier in the atherogenic PAD process might avoid progression to CLTI.

Although I have always been a strong advocate of improved methods of surgical and interventional procedures to improve blood flow to the limbs, I recognize that limitations and risks remain with these procedures. Given the results of TACT, I believe that further investigation of chelation therapy with randomized controlled trials is clearly warranted. I think this should include cases where revascularization with intervention or surgery is successful as well as cases where there was failure to achieve successful revascularization. We must determine primary as well as potentially additive synergistic effects. One must question if this therapy will one day be considered guideline-directed therapy if additional studies confirm these results.

We must leave no stone unturned in our quest to end the need for amputations secondary to ischemic disease. ■