Edetate Disodium Infusions May Benefit Patients With Diabetes and Critical Limb-Threatening Ischemia

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Abstract: Purpose. Patients with critical limb-threatening ischemia (CLTI) remain at a high risk for lower-extremity amputations and mortality. Despite lower-extremity endovascular revascularization and medications, CLTI remains as deadly as many cancers. Lead and cadmium (environmental toxins that can be chelated with edetate disodium) are associated with vascular disease, including peripheral arterial disease (PAD). We report on 9 high-risk CLTI patients with diabetes who underwent edetate disodium-based infusions. The patients had a history of disease progression despite lower-extremity revascularization attempts. Infusions of edetate disodium were offered as an attempt for limb salvage. **Materials and Methods.** Patients with evidence of 2 or more infrapopliteal artery stenoses by imaging and creatinine levels ≤2.0 were offered 40 edetate disodium-based infusions over 8 months. Laboratory safety assessments, clinical history, and lesion photographs were obtained. Arterial duplex ultrasound was obtained in 2 patients before and after the infusions. In a subset of 7 patients, generic and disease-specific quality of life (QOL) was assessed with the SF-36 and Spertus peripheral artery questionnaires. Urine toxic metal content was collected in a subset of patients. Optimal medical therapy and wound care was maintained throughout the infusions. The 7 patients studied at Mount Sinai Medical Center gave informed consent to participate in an institutional review board-approved open-label research project, performed under FDA investigational new drug application 67743 and clinicaltrials.gov NCT03424746. **Results.** Six (out of 9) patients, mean (standard deviation) age 76 (8) years (56% male), had a history of coronary artery disease and PAD. All patients received at least 40 infusions over a median (interquartile range) of 40 (5) weeks. Seven (78%) patients started treatment with an unhealed ulcer or gangrene, and all had wound resolution. In a subset of patients (7), urinary lead excretion increased an average of 3155% and cadmium 918% after the first infusion. The same subset of patients demonstrated an improvement in the disease-specific Spertus peripheral artery questionnaire for QOL of 351% (13.3-60, P=.018), and the overall summary scale improved from 18.4 at baseline to 54, near-average QOL, a gain of 193% (18.4-54, P=.005). The SF-36 was used to characterize general health-related QOL, and this instrument is normalized to a score of 50 for an average population. The SF-36 subscales demonstrated a trend toward improvement in pain (42.5-75, P=.05) and general health of 55% (45-70, P=.089). After a median follow-up of 490 days, no patient underwent surgery for minor or major amputations. One patient underwent lower-extremity endovascular revascularization. Compared to baseline, post edetate disodium urinary lead excretion decreased by 36% (P=.0004) after a median of 51 infusions. No serious side effects related to therapy were reported. No major cardiovascular events occurred. All patients were free of amputation for 18 months after completing treatment. **Conclusions.** The use of edetate disodium infusions increased excretion of the vasculotoxic metals lead and cadmium, and in this small series of patients with diabetes and CLTI, appears safe. There were no limb amputations or cardiovascular events during therapy. Trial to Assess Chelation Therapy (TACT) 3a, a double blind, placebo-controlled, randomized trial to test edetate disodium-based chelation of environmentally acquired toxic metals to reduce cardiovascular events including amputation in high-risk diabetic patients, is currently enrolling and will expand understanding of the role of edetate disodium in patients with diabetes and CLTI.

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Key words: chelation therapy, critical limb-threatening ischemia, diabetes, edetate disodium, limb salvage, peripheral arterial disease

Introduction

Peripheral arterial disease (PAD) affects over 8.5 million Americans.[1] The most severe form of PAD, critical limb-threatening ischemia (CLTI), is defined as rest pain, lower extremity ulcers, and gangrene that leads to over 150,000 nontraumatic amputations annually.[2] Despite minor advances in medical therapy for claudication and major advances in endovascular therapies, the number of nontraumatic amputations remains at a standstill. In 2021, an American Heart Association (AHA) statement on PAD included toxic environmental factors such

as cadmium and lead as nontraditional risk factors for PAD.[3] Urine cadmium level, a surrogate for cadmium body burden, correlates with PAD severity in patients with concurrent coronary artery disease (CAD).[4]

Edetate disodium is an artificial amino acid with a high affinity to divalent cations such as cadmium and lead.[5] Edetate disodium increases urinary excretion of cadmium and lead from body stores in patients with atherosclerosis. In a subgroup of self-identified PAD patients with diabetes in the Trial to Assess Chelation Therapy (TACT), edetate disodium was found to decrease major adverse cardiovascular events by 48% (P=.0069), signaling a potential therapeutic benefit.[6] The present retrospective study reviews the outcomes of 9 patients with diabetes and CLTI who underwent edetate disodium-based therapy for limb salvage. The majority of patients enrolled had nonhealing lower-extremity wounds and numerous endovascular revascularization attempts without improvement in symptoms or quality of life (QOL). Edetate disodium-based infusions were offered as an experimental limb-salvage treatment, as patients had exhausted options for revascularization.

Table 1. Patient characteristics.

Patients	N = 9
Age	76 ± 8.4
Baseline creatine (mg/dL)	0.87 ± 0.25
Sex, female	3 (33%)
Hypertension	9 (100%)
Diabetes mellitus	9 (100%)
Estimated glomerular filtration rate (mg/dL)	71 ± 12.8
Coronary artery disease	5 (56%)
Smoking history	2 (22%)
Ulcer gangrene	6 (67%)
Major amputations	0
Minor amputations	0
Stroke	0
Myocardial infarction	0
Lower extemity revascularization	1
Mortality	0

Patient characteristics at baseline in all patients:
7 patients from Mount Sinai Medical Center and 2 patients from Rosario, Argentina.

Methods

This is a retrospective case series of 9 patients with diabetes and CLTI treated with edetate disodium-based therapy. Seven patients were enrolled at Mount Sinai Medical Center in Miami Beach, Florida, and 2 patients at Instituto Vozzi in Rosario, Argentina. Each patient received up to 50 edetate disodium-based infusions. Patients at Mount Sinai participated in an institutional review board-approved study that was part of an FDA investigational new drug application (67743). Argentine patients were clinical patients, treated as a final effort for limb preservation, based on the results of our previously mentioned pilot study. This study, which includes previously published work,[7-9] contributes to the science by uniting all the CLTI patients treated with a full set of TACT and TACT-like infusions.

Study Population

Patients were age 50 or older with diabetes and a diagnosis of moderate or severe infrapopliteal chronic CLTI (Rutherford Clinical Severity Score 4 or 5) (**Table 1**). Patients had noninvasive evidence of PAD with ankle-brachial index and lower extremity ultrasounds revealing significant stenoses. All patients had diabetes based on a prior diagnosis and the use of hypoglycemic medications, or a hemoglobin A1c >6.5%, or fasting glycemic index of 126 mg/dL or higher.

Study Treatment

All patients received open-label edetate disodium-based infusions through a peripheral IV line over 3 hours. Infusions at Mount Sinai Medical Center contained 3 g edetate disodium adjusted downward based on creatinine clearance, 2 g magnesium chloride, 100 mg procaine HCL, 2500 U unfractionated heparin, 7 g ascorbate, 2 mEq potassium chloride, 840 mg sodium bicarbonate, 250 mg pantothenic acid, 100 mg thiamine, and 100 mg pyridoxine in a volume of 500 mL. Infusions in Rosario, Argentina only included 3 g of disodium ethylenediaminetetraacetic acid, 2 g magnesium, and 7 g ascorbic acid and vitamin B complex. They did not include sodium bicarbonate, procaine HCL, or unfractionated heparin. In both Argentina and the United States, the solution was administered twice weekly for the first 20 infusions and once weekly for infusions 21 to 40. Formal study endpoints were collected at infusion 40. Infusions 40 to 50 were completed once per month in patients at Mount Sinai. All patients received an oral multivitamin preparation.

Urine Metals

Urine metals were collected in the 7 patients at Mount Sinai Medical Center at baseline pre- and post-infusion 1, 20, and 40. Urine samples were analyzed for trace elements using an inductively coupled plasma mass spectrometer.

Quality of Life

QOL surveys were collected in the 7 patients at Mount Sinai Medical Center at baseline, infusion 20, and infusion 40 using the generic, health-related SF-36[10] questionnaire and the disease-specific Spertus peripheral artery questionnaire.[11] Variables are expressed as median (interquartile range). All scores in the QOL questionnaires used are normalized to 50 for a "normal" population.

Figure 1. Wound healing at baseline and post infusion with edetate disodium.

Arterial Duplex Ultrasound

Arterial duplex ultrasound was obtained at baseline, infusion 20, and infusion 40 in the 2 patients in Rosario, Argentina. The same technician and reader analyzed each study to decrease study variability.

Statistical Analysis

Statistical analysis was performed using SAS software, version 9.4. (SAS Institute, Inc.) The baseline characteristics are summarized using percentages for categorical variables and mean and standard deviation (SD) for continuous variables. Urine metals were summarized using means and 95% confidence interval (CI) at baseline, infusion 20, and infusion 40. QOL questionnaire scores were summarized with median and interquartile range.

Results

There were 6 (out of 9) patients, mean (SD) age 76 (8) years (56% male) with a history of CAD and PAD. All patients received at least 40 infusions of edetate disodium. Seven (78%) patients started treatment with an unhealed ulcer or gangrene. All had complete wound healing at the end of the 40-infusion regimen (**Figure 1**). The 2 patients treated in Rosario, Argentina underwent 40 infusions of edetate disodium, while all 7 patients at Mount Sinai Medical Center underwent a total of 50 infusions of edetate disodium-based treatment.

Urinary lead excretion increased an average of 3155% and cadmium 918% after the first infusion (**Figure 2**). No patient underwent surgery for minor or major amputations during the infusion phase, with 1 patient undergoing lower extremity endovascular revascularization. Compared to baseline, post edetate disodium urinary lead excretion decreased by 36% (P=.0004). Arterial duplex ultrasound comparisons before and after infusions with edetate disodium revealed an improvement in arterial flow after 40 infusions **(Figure 3**). No serious side effects related to therapy were reported. No major cardiovascular endpoints were encountered. All patients have remained free of surgical amputation since completing treatment with a median follow-up of 490 days. One patient in Argentina had a spontaneous amputation of a mummified toe, which had been present prior to the onset of therapy.

Standardized QOL or peripheral artery questionnaires were not employed in the 2 Argentine patients. The Mount Sinai subset of patients demonstrated an improvement in the Spertus peripheral artery questionnaire, QOL[11]of 351% (13.3-60, P=.018), and the overall summary scale improved from a median of 18.4 at baseline to 54, a gain of 193% (18.4-54, P=.005). The SF-36 subscales demonstrated a trend toward improvement in pain (42.5-75, P=.05), physical function of 66.7% (45-75, P=.1), and general health of 55% (45-70, P=.089). A significant difference was noted in role functioning/physical of 100% (0-100, P=.005). All QOL measures can be found in **Table 2**.

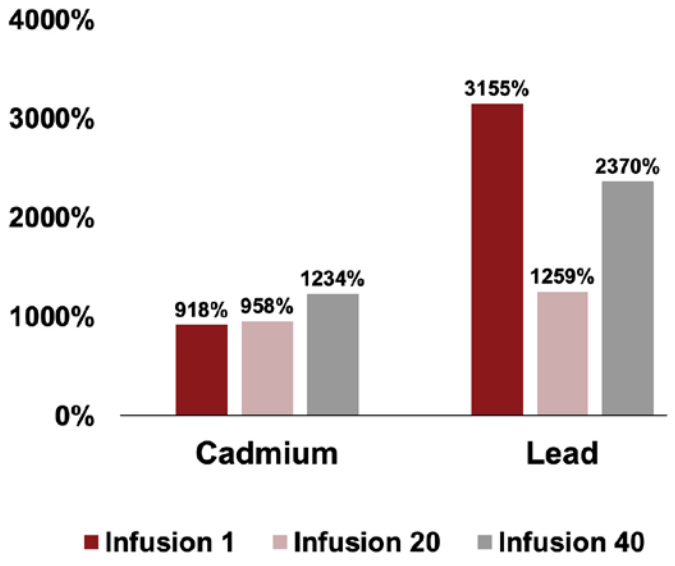
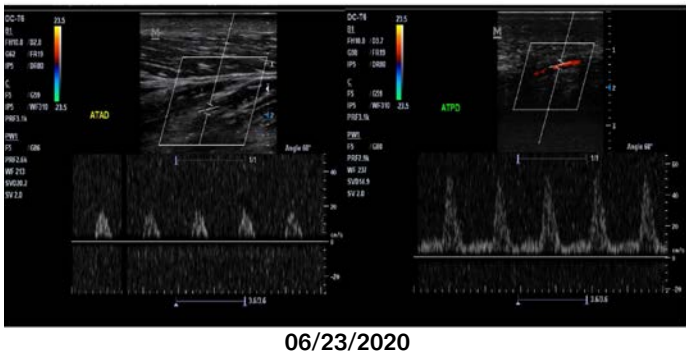


Figure 2. Percent increase over baseline in urinary cadmium and lead excretion following edetate sodium infusion.



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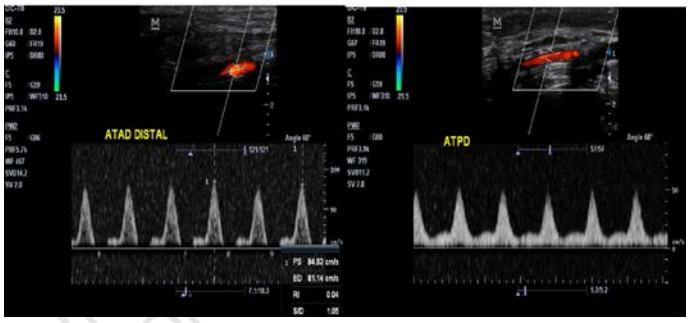

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Figure 3. Lower extremity duplex ultrasound. Baseline arterial duplex ultrasound of the anterior tibial artery reveals total vessel occlusion, with follow-up duplex ultrasound demonstrating increased blood flow to the previously occluded vessel.

Discussion

When progressive PAD ends in CLTI, it may account for over 150,000 nontraumatic lower extremity amputations in the United States.[1] The healthcare costs of CLTI patients in the United States averages over $300 million annually. Hospitalizations in CLTI patients exceed 60% in 6 months, revascularizations 90%, and an overall annual mortality rate up to 40%. Although there have been advancements in medical treatment such as statins, antiplatelets, and endovascular procedures, the rate of lower-extremity amputations has been relatively stagnant. Over the last several decades, epidemiological studies have identified ubiquitous environmental toxicants, especially lead and cadmium, as linked to atherosclerosis, including PAD. In 2021, in recognition of the strength of these epidemiological data, the AHA identified nontraditional risk factors in PAD, which included contaminant metals such as lead and cadmium.[3] Our work suggests that a reduction in these toxicant metals may have beneficial effects for a previously untreatable condition.[5] In this retrospective case series, adjunctive therapy with edetate disodium improved nonhealing lower extremity ulcers, decreased limb amputations, and improved QOL, including a 76% reduction in pain.

Lead and cadmium are acquired from the environment via the respiratory or gastrointestinal tracts. After absorption, these metals are deposited in many tissues including bone for lead, liver, and kidney, and arteries for cadmium. Both metals accumulate in the body for decades. Mounting epidemiologic and mechanistic evidence links lead and cadmium to the progression of atherosclerosis. Lead and cadmium may promote atherosclerosis and PAD by several mechanisms including endothelial dysfunction, vascular smooth muscle cell proliferation, activation of proinflammatory signaling pathways, oxidative stress, and direct vascular tissue damage.[16] In a study of 728 participants from the 1999-2000 National Health and Nutrition Examination Survey (NHANES), Navas-Acien et al reported that subjects with PAD had a 36% higher concentration of urine cadmium compared with subjects without PAD.[12] Moreover, compared to the 25th percentile of urine cadmium, subjects in the 75th percentile had a threefold increased prevalence of PAD (odds ratio [OR] 3.05, 95% CI, 0.97-9.58). In 2018, our group examined the relationship between urine cadmium levels in patients with CAD and their PAD severity, including CLTI. The study found urinary cadmium levels were lowest in patients with CAD without PAD, higher in patients with CAD and PAD (with no CLTI), and highest in patients with CLTI (0.37 ± 0.19, 0.56 ± 0.34, and 1.56 ± 2.33 µg/g of creatinine, respectively, with P=.009).[4]

Cadmium is not the only metal contaminant associated with PAD. The 1999-2000 NHANES found that the prevalence of PAD was nearly 3-fold higher in participants in the highest quartile of blood lead (>0.14 µmol/L) compared with those in the lowest quartile (<0.07 µmol/L) (adjusted OR 2.88, 95% CI, 0.87-9.47).[13] Likewise, a study that included 16,609 subjects from NHANES 1988-1994 and 9961 subjects from NHANES 1999-2002 found that subjects in the highest quartile of blood lead concentration (≥2.47 µg/dL) were 1.9 times more likely to have PAD (1.92, 95% CI, 1.02-3.61).

Table 2. Quality of life questionnaires.

Questionnaire	Baseline	Infusion 20	Infusion 40	*P* value*
Spertus peripheral artery questionnaire				
Physical limitation	13.9 (5.6-25.0)	44 (36.1-47)	44.4 (33-51.4)	.2
Symptom stability	33.3 (33.3-41.7)	50 (41.7-58.3)	50 (25-50)	.05
Symptoms	22.2 (19.45-38.95)	50 (47.2-58.35)	55.6 (17.0-75.0)	.06
Social limitation	44 (11.1-52.8)	44.4 (41.4-58.4)	53.3 (42-72.25)	.1
Treatment satisfaction	60 (43.33-76.7)	80 (53.3-80)	60 (53.3-73.3)	.3
Quality of life	13.3 (9.9-30)	53.3 (50-53.3)	60 (33.3-66.4)	.02
Summary scale	18.4 (12.7-30.9)	49.4 (48.1-54.6)	54 (34-59)	.005
SF-36				
Physical function	45 (28.8-60)	58 (37.5-80)	75 (57-80)	.1
Role functioning/physical	0 (0-35)	75 (17.5-87.5)	100 (55-100)	.005
Role functioning/emotional	33.3 (0-66.7)	100 (83.4-100)	100 (61.4-100)	.2
Mental health	45 (32.5-88)	55 (50-88.5)	80 (55-93.5)	.4
Emotional well-being	80 (74-80)	84 (68-96)	80 (66-96)	.8
Social functioning	37.5 (12.5-75)	75 (37.5-100)	75 (50-93.8)	.1
Pain	42.5 (10-50)	80 (53.8-85)	75 (46.3-78.8)	.05
General health	45 (45-64.4)	60 (44.4-75)	70 (40-82.5)	.08

Quality of life questionnaires including the Spertus peripheral artery questionnaire and SF-36. Only includes the 7 patients from Mount Sinai Medical Center. Variables expressed as median (interquartile range). *Nonparametric Friedman test.

Medical interventions to decrease the body burden of metal contaminants may be beneficial. In the TACT, which randomized 1708 patients with a history of myocardial infarction to edetate disodium or placebo, individuals with CAD, PAD, and diabetes were seen to have the most benefit with treatment. There was a decrease in the composite major cardiovascular endpoint of TACT, which consisted of death from any cause, coronary revascularization, and hospitalization for angina of 48% (95% CI, 0.30-0.92, *P*=.0069).[14] The present small study in patients with diabetes and CLTI suggests that a 40-infusion regimen of edetate disodium may safely decrease lower extremity amputations and improve QOL. A recently published exhaustive systematic review of edetate disodium for vascular disease reported a signal of benefit for patients with diabetes.[15] Altogether, these observations suggest that edetate disodium could potentially constitute adjuvant therapy for the treatment of atherosclerotic lower-extremity disease.

There are various study limitations. This is a small retrospective study of 9 patients; thus, any findings are hypothesis-generating and should not be brought to the clinical arena without careful thought. Larger studies with edetate disodium in high-risk patients, such as in TACT2 in patients with diabetes and myocardial infarction, and TACT3a in patients with diabetes and CLTI, will further explore potential benefits of edetate disodium. Although all patients at Mount Sinai and Rosario, Argentina received edetate disodium-based infusions, the overall infusion ingredients were not the same in the 2 countries. Finally, there was no systematic assessment of blood flow. The 2 patients in Rosario had improvements in blood flow as measured by arterial duplex ultrasound, but such clinical data are at best only suggestive.

Conclusion

In patients with diabetes and CLTI with no options or failed attempts at endovascular revascularization, edetate disodium appears safe and may lead to limb salvage. Both research and clinical experience will be necessary before widespread implementation of this therapy. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

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