

**Varena M, Zucchi F, et al. Intravenous Clodronate in the Treatment of Reflex Sympathetic Dystrophy Syndrome. A Randomized, Double Blind, Placebo Controlled Study. J Rheumatol 2000;27(6):1477-1483**

Design: Randomized clinical trial

Population/sample size/setting:

- 32 patients (13 men, 19 women, mean age 56) treated for CRPS-I at departments of rheumatology and endocrinology in Milan, Italy
- Eligible patients had definite CRPS based on pain with allodynia and/or hyperpathia, tenderness, vasomotor changes and/or hyperhidrosis, dystrophic skin changes, and swelling
- All patients had bone scintigraphy showing increased uptake
- Pregnancy was apparently the only exclusion criterion

Main outcome measures:

- Randomization was to IV clodronate (n=15) or saline placebo (n=17)
- IV clodronate was administered at a dose of 300 mg daily for 10 days diluted in 250 ml of normal saline; the placebo group had only the saline infusion
- Main outcome was pain VAS at 40 days compared with baseline VAS
- Additional measurements of VAS were done at 90 and 180 days
- At the end of 40 days, the patients and clinicians were unblinded, and the placebo group was given IV clodronate in the same schedule as the clodronate group during the double-blind phase of the study
- Secondary outcomes were clinical global assessment and a verbal report of overall efficacy (worsening/no change, slight improvement, significant improvement, excellent improvement/no pain)
- Blood and urine measurements were done at baseline and 40 days later for markers of osteoclast activity (crosslinked N-telopeptide=NTx) using monoclonal antibodies
- 31 patients completed the study; 1 died in a motor vehicle accident
- At day 40, the clodronate group had significant improvements from baseline in all clinical variables, with pain VAS declining from a mean of 58.4 to 22.3; the placebo group registered a smaller VAS improvement at 40 days, from 62.5 to 56.4
- 11 clodronate patients reported significant improvement at 40 days; no placebo patient reported significant improvement
- During the open label phase, the placebo group responded to clodronate in a manner similar to that of the clodronate group during the double-blind phase; the mean VAS decreased to 22.6, with 10 patients reporting significant improvement and 2 reporting excellent improvement/no pain 40 days after receiving clodronate
- At 90 and 180 days, the improvements continued to accrue; the overall percentage decrease of pain VAS from baseline was 93.2%

- NTx was elevated in only 7 of 32 patients at baseline, but there were significant inverse correlations between baseline NTx and percentage improvements in pain VAS at 90 and 180 days
- Patients tolerated clodronate well; 3 patients had transient hypocalcemia, but none had clinical symptoms

Authors' conclusions:

- A 10 day course of IV clodronate is better than placebo in reducing symptoms of CRPS, and induces rapid and lasting improvement
- The role of clodronate in influencing osteoclast activity is probably not the only mechanism of action; cytokines and mononuclear phagocytes are likely to be involved as well
- The predictive value of NTx for response to clodronate is not clear

Comments:

- Although success of blinding is not reported, the randomization appears adequate and risk of bias is probably low
- Exclusion and inclusion criteria are not spelled out, but the patients were recruited consecutively from the rheumatology day clinic, the orthopedic services, and the emergency department; it would be surprising if 37 consecutive patients all had positive bone scans, but the referrals may have been made on this basis

Assessment: adequate for evidence that clodronate effectively reduces pain in patients with CRPS and positive bone scintigraphy