Rauck RL, Eisenach JC et el. Epidural Clonidine Treatment for Refractory Reflex Sympathetic Dystrophy. Anesthesiology 1993;79:1163-1169.

Design: Crossover randomized clinical trial

Brief summary of findings:

- 26 patients (mean age 38, 16 upper, 10 lower extremity symptoms, men/women not reported) were treated for CRPS at a university pain control center in North Carolina
- RSD was diagnosed by history of trauma or surgery followed by burning, throbbing, or aching pain plus sudomotor changes, vasomotor instability, or contractures
- All had been diagnosed with sympathetically mediated pain, supported by relief obtained with sympathetic blockade
- Some had additional diagnostic tests, such as three phase bone scans and ice water stress testing
- Exclusion criteria were renal insufficiency (creatinine> 3..5), heart block greater than first degree, concurrent use of alpha-2 adrenergic agonists or alpha antagonists, pregnancy and hypersensitivity to clonidine
- All patients received an epidural catheter inserted via the C7-T1 or the L2-3 interspace, and advanced into the epidural space
- Patients were in the hospital for three days, and were injected on subsequent days in random order with normal saline, 300 mcg clonidine, or 700 mcg clonidine in a 10 ml volume through the epidural catheter
- Both patient and investigator were blinded to injectate
- VAS pain scores were obtained at 20, 40, 60, 120, 180, 240, and 360 minutes after the injection; blood pressure and heart rate were monitored frequently
- Both doses of clonidine reduced VAS pain by a similar amount within 20 minutes of injection, but placebo was not effective; pain relief lasted up to the final measurement at 6 hours after the injection
- Heart rate and blood pressure were reduced by both doses of clonidine by similar amounts, but were not reduced by saline placebo
- After the three-day crossover trial, 19 of the 26 patients who responded to clonidine but not to placebo and who wished to continue, received continuous epidural clonidine at a rate of 20 mcg/hr, which was titrated at weekly intervals, depending on pain relief, sedation, or hypotension; the shortest duration of continuous infusion was 7 days and the longest was 225 days
    - Mean pain VAS was 7.9 before treatment, and 5.1 during treatment
    - Infections occurred in 6 of the 19 patients during continuous clonidine infusion;
    - 4 infections occurred within 1 month of catheter insertion; 2 had superficial cellulitis, 1 had superficial abscess, 1 had a febrile illness with *Staph epidermidis* recovered from CSF
    - 2 infections occurred 4.5 and 7.5 months after catheter insertion, requiring catheter removal and oral antibiotics

Authors' conclusions:

- These data demonstrate acute efficacy and chronic efficacy from epidural clonidine with chronic RSD
- Because of the frequency of infection, it appears imprudent to leave temporary catheters for longer than 2 weeks

Comments:

- This is best described as a pilot study, with small numbers of patients and short periods of observation
- The three injections, saline, 300 mcg clonidine, and 700 mcg clonidine, were given in random order; this makes it a crossover trial, but some important data are not reported which are needed to interpret crossover trials
    - There is no report of either period effects or carryover effects
- Functional improvement is not reported
- Although the 300 and 700n mcg clonidine doses were similarly effective, a Dose x Time interaction is reported; this should probably be reported as a Treatment x Time interaction, since a dose of 0 mcg clonidine appears to be entirely responsible for the "Dose" by time interaction
- McGill Pain Questionnaire data were obtained, and were analyzed separately because of missing data; the number of patients with missing data was not reported
- The number of infections with prolonged clonidine infusion should be seen as a cause of great concern for the use of epidural clonidine in clinical practice; this can be seen as a satisfactory case series, which can furnish evidence about complication rates of an intervention

Assessment: Inadequate for effectiveness of clonidine (no functional data, period of controlled observation only 6 hours, no data on carryover or period effects)

Adequate for evidence that the risk of infection with prolonged epidural infusion of clonidine is unacceptably high