Finch PM, Knudsen L, Drummond P. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. Pain 2009;146:18-25.

Reviewed, no change to conclusions January 2017

Design: Randomized crossover trial

Population/sample size/setting:

- 20 sequential patients (6 men, 14 women, mean age 40) treated fro CRPS at a small private pain center in Australia
- Each patient met the 1994 IASP criteria for CRPS, and 17 met the Budapest criteria; 12 were affected in the upper extremity and 8 in the lower extremity
- Sensory testing was done by a single examiner on the most hyperalgesic dorsal aspect of the symptomatic limb, with testing of the corresponding part of the other limb; sensory testing was also done on each side of forehead
    - Light touch threshold estimated with Von Frey filaments
    - Pressure-pain thresholds were assessed with a spring-loaded algometer
    - Sharpness was rated with a firm nylon bristle for punctate stimulation
    - Light stroking was done with a small brush; sensations described as sharp, scratching, or uncomfortable were classified as allodynia
    - Thermal thresholds were determined with contact probes which started at 32° C and then were changed by 0.5°C to a maximum of 50° or a minimum of 5°C for warm and cold thresholds respectively
- 0.5 ml of racemic ketamine HCl 10% was applied in a polymeric lecithin gel vehicle by one of the researchers while 0.5 ml of the vehicle alone was applied to the other limb; the creams were labeled A or B using a code known only to the pharmacist
- The main outcome was a comparison of the above sensory tests, performed before and 30 minutes after the application of the creams
- For the first 10 patients, venous blood was drawn 1 hour after the application of the creams and assayed for both ketamine and norketamine
- The application of the creams was repeated 7 to 23 days after the first applications, with ketamine and placebo applied to the opposite limbs, allowing for comparison of ketamine and placebo in the same patients
- Pressure-pain (algometer) and light touch thresholds did not differ significantly between ketamine and placebo cream applications; both creams increased the pressure-pain threshold in the symptomatic limb
- Allodynia significantly decreased after ketamine application; the proportion of symptomatic limbs with an allodynic response to light stroking decreased from approximately 85% to about 55% (judging from Fig. 1); p=0.049
- Ketamine also inhibited pain from punctate stimulation; judging from Fig. 2, the sharpness rating in the symptomatic limb (scale from 0 to 10) decreased by about 1 point when the skin was pricked three times (p=0.005)

- Brush allodynia was also observed on the side of the forehead ipsilateral to the affected limb in about 60% of patients (Figure 4); after the application of ketamine, this was reduced to about 40% (p=0.042)
- Neither ketamine nor norketamine could be detected in the plasma of the first 10 patients, and assays were then discontinued

Authors' conclusions:

- Ketamine inhibited allodynia and punctate hyperalgesia in the symptomatic limbs of patients with CRPS
- It is likely that the response to ketamine involved peripheral NMDA receptors
- Systemic absorption of ketamine does not occur after topical application
- The hemisensory disturbances of CRPS may extend to the face, perhaps involving supraspinal nociceptive processing (thalamic or cortical); the finding that ketamine inhibited brush allodynia in the ipsilateral forehead needs to be confirmed in a larger number of patients
- Since only one dose of ketamine was administered at only one time point, further controlled studies are needed to determine the therapeutic response to ketamine
- Although ketamine did not lead to pain reduction, future research may lead to its use as an adjunct to sensory-motor retraining programs when CRPS patients suffer from manifest allodynia

Comments:

- Interpretation of the study is limited by the omission of some information normally expected in a clinical trial which is to be applied to daily practice
    - Participant recruitment and eligibility are scantily described; inclusion and exclusion criteria, if any, are missing from the methods section
    - There is no information about which, if any, interventions for CRPS had been attempted in the enrolled participants, nor is it clear if patients were referred because of the failure of previous treatments
    - Effect sizes are not presented numerically but only in the form of bar graphs, requiring the reader to approximate the treatment responses; p values are not a substitute for effect sizes
- The outcome assessments were done 30 minutes after a single application of ketamine by a research assistant
    - This provides no guidance as to how often ketamine would be applied in clinical practice, how long it would need to be used, or how long its anti-allodynic effects could be expected to last
    - The outcomes consist of specialized sensory testing; this provides little information about the effect of ketamine on how well patients function and perform daily activities
- There was a washout period of at least 7 days between ketamine and placebo (or the reverse); this was done in order to allow for the removal of all ketamine and its metabolites from the skin
    - Crossover trials do require a washout period between active and control interventions, but more information is needed here

    - The washout period was done to eliminate potential pharmacokinetic carryover from one treatment period into the next, but it is also important to report on whether there was any pharmacodynamic carryover from one treatment period into the next (i.e., did each patients have the same sensory thresholds at the beginning of the second treatment session that were present at the beginning of the first treatment session?)
- In Figure 1, it is apparent that ketamine reduced the proportion of patients with allodynia in the affected limb, but ketamine did not eliminate allodynia in a majority of patients
- In Figure 1, it appears that there was a placebo response of zero; while there is no law that requires that a placebo response be present, it is unusual to have the response be entirely absent
- In Figure 2, ketamine reduces the sharpness response to punctate stimulation in a statistically significant manner (the p values for the Wilcoxon test and the ANOVA are different, but this is not a problem); however, the actual effect size appears to be quite small and of limited clinical relevance
- It is of pathophysiological interest to observe allodynia on the side of the forehead ipsilateral to the affected limb, but some findings require further elaboration
    - In Table 3, the pain-pressure threshold on the contralateral side of the forehead is 524 g, which is less than half of the threshold on the healthy limb (1101 g in Table 2)
    - This would suggest that the forehead is more sensitive to pressure than the limb; this is easily plausible, but should be mentioned in the discussion
- Presumably no adverse effects occurred; an explicit mention of this should have been made
- The study is sufficient (as a proof-of-principle study) to suggest that topical ketamine warrants more study in a larger number of patients with longer follow-up and more reporting of functional outcomes, but is not sufficient to recommend topical ketamine as an intervention for most patients with CRPS

Assessment: Inadequate for evidence about the effectiveness of topical ketamine for CRPS (eligibility/exclusion criteria insufficiently described; outcome measurement is done only once 30 minutes after application of ketamine; most patients do not eliminate allodynia; effect size unclear but appears to be small; insufficient information to make guideline recommendations about appropriate frequency and length of use