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Commentary

Intravenous ketamine for CRPS: Making too much of too little?

Several publications and reports have recently advocated the use of intravenous ketamine infusions for the treatment of chronic pain. In Pain, Schwartzman and colleagues present the results of a randomised controlled trial where 19 patients with CRPS were treated with ketamine or placebo infusions [9]. The trial was stopped prematurely before half of the planned number of patients was included, reportedly because the non-trial experience with higher doses of ketamine suggested they would obtain greater efficacy in a new trial with higher doses. The paper concludes that intravenous ketamine administered in an outpatient setting resulted in statistically significant reductions in many pain parameters.

Some pain clinicians regularly use ketamine infusions in their clinical practice, so it is important that this practice is proven in randomised placebo-controlled trials. The trouble is that randomised trials with methodological shortcomings can mislead us. In clinical research, about 15% of initial results are contradicted by further research; while in 15% much stronger effects are found [4]. When journals can publish articles with the title "Why most published research findings are false" we have a duty to be cautious, and take new findings with a pinch of salt [5]. The size of the pinch is inversely proportional to the quality of the study.

This study was prematurely terminated, leaving only groups of 9 and 10 patients. No primary efficacy variable is clearly specified. The process of randomisation is not described, the trial is not convincingly blinded, and withdrawals are not described, so the analysis is per protocol, rather than intention to treat. The study would score only 2/5 on the Oxford quality scale [6], and 5/16 on Oxford Pain Validity Scale [11]; scores like this have been associated with systematic bias.

In figuring out how the evidence stacks up for ketamine infusions, and how we should regard it, it behoves us to consider those influences likely to falsely enhance a study. Research [5] suggests that studies are more likely to be false when:

1. Studies are small; small studies tend to overestimate treatment effects. Here there were just 19 patients.
2. Effect size is small. Here the biggest difference in pain in the most affected area amounted to 1.5/10, when standard deviations were three times that size, suggesting huge between patient variability.
3. Many unselected relationships are tested. Here a minimum of 23 different tests was applied on five different occasions. Most of the time statistical significance was at the 5% level, without adjusting the significance level for multiple testing. It would have been more appropriate to adjust the level of significance by a factor of at least 10, of 0.005 rather than 0.05. Only a few sporadic statistical significances would have remained.

A similar trial [10] also found that iv S(+) ketamine reduced pain scores in CRPS patients, with a statistical difference from placebo 11 weeks after the initial treatment. Despite improved pain scores, there was no difference between groups regarding function. This was a well-performed trial, although blinding was compromised because 28 of 30 patients in the ketamine group correctly guessed treatment assignation.

Efficacy issues aside, these two papers [9,10] raise a number of questions. What do the authors consider is a feasible treatment plan for patients with CRPS? Do they envisage repeated intravenous infusions? Ketamine is neurotoxic, and a drug of abuse. The NMDA receptor is involved in learning and memory processing and frequent abuse of ketamine has been shown to cause long-lasting memory impairment and altered prefrontal dopaminergic function [1,8]. Although not confirmed in studies in healthy humans, repeated administration of ketamine in sub-anaesthetic doses is reported in animal studies to cause sensitization, a characteristic of drugs such as cocaine [13]. If there are risks associated with repeated intravenous treatments in a chronic pain patient population, we need at least some safety data before repeated intravenous infusions of ketamine can be considered a routine treatment option.

Another question concerns total treatments costs for the patient and healthcare systems. Compared to sympathetic blocks, the economic implications of four-hourly ketamine infusions daily for 10 weeks [9] or a four-day infusion requiring 5 days hospital admission [10] are clearly considerable.

In their discussion section, Schwartzman et al. claim that, in their experience, "only a 5 day intravenous regimen with ketamine at anaesthetic doses with midazolam and clonidine...provides complete remission of CRPS symptoms...in approximately half of the subjects". This statement is based on an open label study involving high total doses of ketamine in 20 patients, requiring endotracheal intubation, and 5 days of intensive care treatment [7].

Current algorithms for CRPS treatment emphasize that the optimal approach is multidisciplinary [3] and there are other options in many patients. A recent trial reported that topical ketamine reduces allodynia in patients with CRPS, albeit with small numbers [2].

Current evidence indicates that ketamine is a useful drug for refractory pain in certain clinical settings, but optimal treatment regimens for chronic pain are lacking. While it is important to establish efficacy data through high quality trials, it is equally important to focus on safety issues, especially in conditions like CPRS, where large numbers of patients are not available for trials. A recently published topical review on ketamine for chronic pain was used to support a plea that ketamine be available not only to anesthesiologists, but to "the entire medical community" [12]. Schwartzman uses the same reference to support the statement

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that ketamine "has a well-established role in the treatment of acute and chronic pain". Both seem to have missed the point that the basic message of the topical review was cautionary.

Conflict of interest statement

There are no conflicts of interest.

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