Ketamine for Chronic Pain

Old Drug New Trick?

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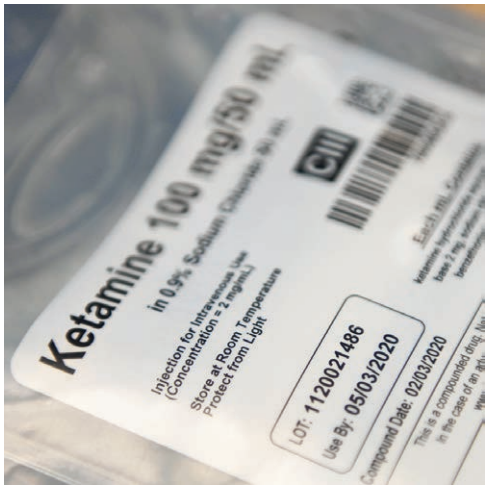
Ketamine ranks among the most basic pharmacologic tools of the anesthesiologist. Approved in 1970 as an anesthetic agent derived from phencyclidine, the drug quickly proved its worth in battlefield settings where maintenance of hemodynamic stability was a prime requirement.[1] To this day the drug is valued for use in unstable patients, in those with reactive airway disease, and in situations where sedation, analgesia, or induction is required without having intravenous access. Those indications alone provide ketamine a prominent and durable position in our pharmacologic armamentarium. However, after decades of use, and illicit abuse for its ability to provide a dissociative high, the drug may still have a few tricks to reveal, including the treatment of psychologic disorders, the prevention of chronic postoperative pain, and, as addressed by Pickering *et al.*[2] in this issue of Anesthesiology, the treatment of chronic pain when infused at low doses.



"Ketamine is exceedingly useful in … anesthesia and … psychiatry. Despite these successes, we struggle to identify clear roles for ketamine in patients affected by chronic pain."

The demonstration of the ability of low-dose ketamine (~0.5 mg/kg infused over about an hour) to improve mood in those with treatment-resistant depression, if only for a week or so after administration, has received tremendous attention. Observation of this antidepressant activity led to the development of the S-enantiomer of the original clinical formulation RS-ketamine, esketamine, for intranasal delivery and the approval of the drug for treatment-resistant depression by the U.S. Food and Drug Administration in 2019. Interestingly, it is not clear that the antidepressant effects of either ketamine or esketamine rely entirely on *N*-methyl-D-aspartate (NMDA) receptor blockade because multiple other ion channels and receptors seem to be regulated by these drugs or their metabolites.[3] Beyond uncertainty over mechanism, data regarding effectiveness and toxicity of ketamine and esketamine with repeated dosing are very limited, and the lack of clearly defined "exit strategies" from frequent ketamine and esketamine administrations has been described as a major unmet need.[4] So, although serious issues remain regarding the appropriate use of these drugs, the conversation is at least transparent, and the claims of effectiveness are generally sober.

Closer to the practice of anesthesiologists, ketamine use has traveled the entire distance of the anesthetic process from induction agent, to intraoperative adjunct anesthetic, to postoperative analgesic. In fact, it is believed that through the ability of ketamine to prevent central sensitization, infusions of ketamine started intraoperatively and continued into the early postoperative period might prevent chronic postoperative pain, a vexing problem impacting approximately 20% of surgical patients overall but a much higher percentage of patients undergoing surgeries in which nerve injury is likely.[5] Evidence exists for at least modest activity against chronic postoperative pain, and the ongoing ROCKET (Reduction Of Chronic Post-surgical Pain with Ketamine) trial involving 8,000+ subjects will hopefully clarify the issue further.[6] Although we have not fully defined the best roles for ketamine in the care of surgical patients, the fund of good quality data is already large and is becoming more complete. Again, a robust conversation regarding clinical utility is being driven largely by high-quality research.

Image: J. P. Rathmell.

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Regrettably, not all potential new indications for ketamine are as promising or have been as deliberately explored. In this issue of Anesthesiology, Pickering *et al.*[2] address yet another potentially very-high-impact use of ketamine, as a treatment for refractory chronic neuropathic pain when infused at low doses. This study has many positive attributes. The crossover design of the ketamine trial, although challenging to execute, allowed patients to act as their own controls thus enhancing the power to find positive effects of ketamine on pain. Additional factors, such as the careful definition of "neuropathic" pain using the Douleur Neuropathique 4 neuropathic pain questionnaire, provided focus on a type of pain particularly strongly associated with central sensitization and NMDA receptor participation.[7] Not only was ketamine tested, but the combination of ketamine and magnesium was included in their triple crossover design. This was rationalized by the known pharmacology of magnesium as an extracellular NMDA receptor blocker that may potentiate or add to the analgesic effects of ketamine, and itself has been explored as an analgesic agent for some types of chronic pain such as postherpetic neuralgia.[8] Despite the strong rationale for testing ketamine and the combination therapy, the present study failed to identify an effect of ketamine for its primary endpoint of area under the curve of daily pain intensity for a period of 35 days after infusion. Likewise, several secondary endpoints of emotional health, sleep, and other outcomes were likewise unimproved. Overall, it is difficult not to regard these findings as discouraging for the use of one-time low-dose ketamine infusion for the treatment of a type of pain that should, in theory, be particularly amenable to the approach.

The use of ketamine for chronic pain and other maladies has drawn comparisons to the Wild West as use of these infusions is random and poorly regulated.[9] Ketamine clinics are now commonplace, advertising treatment of depression, anxiety, bipolar disorder, posttraumatic stress disorder, and, of course, chronic pain. Websites for these clinics typically offer testimonials of miraculous responses. Initial consultations may be free, but the infusions are often a cash deal. On the other hand, scientific reviews universally lament the lack of definitive evidence of effectiveness for low-dose ketamine infusion, at least for chronic pain. For example, in a recent carefully conducted meta-analysis designed to define the utility of ketamine infusions for chronic pain, only seven studies met inclusion criteria, comprising a mere 211 total patients. Very small sample sizes, risk of bias, and other methodologic issues were noted, and only short-term (2- to 14-day) benefits from the infusions were suggested although with significant reservations.[10] Lack of clarity on best dose, favorable indications, and potential use of adjuvants were all cited as problems with the current body of data. Although downplayed when discussing single low-dose administrations, ketamine clearly has a significant dose-dependent side effect profile comprising central nervous system as well as cardiovascular problems related to sympathetic stimulation and longer-term problems associated with chronic use and abuse like hepatotoxicity, cystitis, behavioral changes, structural changes in the brain, and substance use disorder.[11] Very little long-term outcome or safety data are available for chronic pain patients receiving ketamine.

In response to the burgeoning use of ketamine in the absence of guidance, the American Society of Anesthesiologists (Schaumburg, Illinois), along with American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania) and American Academy of Pain Medicine (Chicago, Illinois), issued guidelines in 2018 for the use of intravenous ketamine for chronic pain.[9] These are a mandatory read for all anesthesiologists using or considering use of ketamine for a chronic pain indication. The guidelines can be credited with digesting and presenting an unruly literature and placing guardrails on the use of ketamine infusions. Although the authors were able to provide general guidance on contraindications, useful training, and reasonable approaches to monitoring, the substrate of information was inadequate to provide definitive guidance on patient selection, optimal dosing, or estimation of risks with ongoing treatment.

Although it would be easy enough to say, "more research is needed" and simply go on infusing chronic pain patients hoping that data will one day appear supporting what we have been doing for years, it may be time for a more cautious reassessment of ketamine in our chronic pain treatment arsenal. The following may be important steps:

1. Even the most optimistic practitioners seldom speak of ketamine cures; committing to a low-dose ketamine trial is committing to the potential for long-term IV treatment perhaps at a multiple-infusions-per-month rate. We should develop meaningful data on the risks as listed above *versus* total dose received with some attention to comorbidities that might predispose patients to adverse outcomes like cardiovascular disease, liver conditions, or substance abuse histories. Patient registries might be a good option here.
2. We need to decide what constitutes an adequate response to consider repeating the therapy or committing the patient to ongoing infusions. It would be enormously helpful to reach some rational consensus on what defines successful therapy based on pain relief, function, sleep, quality of life, and other measures endorsed for evaluation of outcomes for chronic pain treatments. This consensus should include both the magnitude of the effects and, critically, the minimum significant duration of improvements.
3. It would be helpful to have an empirically supported approach to selecting ketamine dose. Very low (less than about 0.5 mg/kg) doses have simply not reliably demonstrated much effect for most indications. The architects of recently released ketamine guidelines suggest at least 80 mg over an hour as a start, but the most successful studies have used much larger doses over a days to weeks,

sometimes requiring hospital admission and intensive monitoring. Regrettably, the use of higher doses of ketamine over longer periods of time would change many clinical practices significantly, and risks to patients would surely increase. Perhaps a dose ladder protocol would be rational, balancing clinical improvement with tolerability.

4. Chronic pain management is arguably at its most effective when multidisciplinary. Let's avoid using ketamine *a la carte* and include the drug only as a part of a treatment plan that optimizes other (nonopioid) medications, activity-based therapies, behavioral approaches, and additional options as appropriate to reduce reliance on a single intervention. Identifying the optimal combination of ketamine and other therapies will be a difficult but important task.

There is little doubt that ketamine is exceedingly useful in the practice of anesthesia and now perhaps in the field of psychiatry. Despite these successes, we struggle to identify clear roles for ketamine in patients affected by chronic pain. The unbridled use of ketamine "for what ails you" threatens to undermine the goal of understanding the proper uses of the drug, including long-term risks, before releasing it on large populations of patients. Deemphasizing use of infused ketamine until and unless we can determine how and in whom to use the drug is in the best interest of patients and ultimately the field of pain management.

Competing Interests

Dr. Clark is a consultant for Teikoku Pharma USA Inc. (San Jose, California).

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