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Promising Data With Ketamine in Chronic and Phantom Limb Pain

Nancy A. Melville | May 17, 2016

AUSTIN, Texas — As clinicians work to find alternatives to opioids in the treatment of chronic pain, some are finding success with ketamine, a drug that has also recently gained much interest in the treatment of severe depression.

"I have been using oral ketamine for my chronic pain patients and have been seeing amazing results," said Lucinda Grande, MD, from the University of Washington's Department of Family Medicine in Seattle told *Medscape Medical News*.

"I will use oral ketamine for chronic pain patients who are not on opiates yet as kind of a technique to prevent them from getting on to opiates," she said. "And most people in the study who were already on opiates were able to get down to a lower dose with the use of ketamine."

She discussed early results to date here at the American Pain Society (APS) 35th Annual Scientific Meeting.

Conventionally used as an intravenous anesthetic, oral ketamine has been shown in some small observational studies to offer benefits when used off label to treat chronic pain. However, randomized controlled trials on the approach have been lacking.

Dr Grande said that with her own success in the treatment of more than 300 patients with chronic pain during the past 5 years with oral ketamine, she decided to conduct her own randomized trial.

For the study, the researchers randomly assigned 32 opioid-tolerant patients to oral ketamine, up to 64 mg per day, or an inactive placebo for 2 weeks.

In terms of improvements in key measures of Brief Pain Inventory (BPI), Patient Health Questionnaire-9 (PHQ-9), and Clinical Global Impression–Improvement of Condition (CGI), recorded by patients, CGI scores of "much improved" or "improved" measures of pain were reported by 10 of 16 patients in the ketamine group compared with 6 of 16 in the placebo group, which was not a statistically significant difference.

The ketamine group showed trends toward greater improvement in terms of the daily log of interference with activity, minimum pain, and average pain on the BPI for pain relief from medications (increase of 13% in the ketamine group vs 7%; $P = .44$) and on the PHQ-9 (decrease of 4.5 vs 3.3; $P = .49$).

Adverse effects among the patients were reportedly rare and minor.

Dr Grande said the lack of a robust response did not reflect her clinical experience and may have been a result of the dose used in the study.

"I was expecting to see the same results that I see clinically, but the study didn't show a statistically significant difference between the groups, and I think it is because I chose too low of a dose for the study, unfortunately."

Stronger improvement was demonstrated, however, in an open-label titration of ketamine over 7 months, in which patients were treated with a higher dose.

Among 15 of 19 patients who responded to a survey in the open-label phase, the average ketamine dose was 101 mg/day (range, 16 to 256), and 11 of the 15 patients reported CGI that was "much improved" or "improved."

Importantly, opioid dose decreased in 9 of the 15 patients.

"In the open-label part, among patients still on ketamine, 75% were improved and the ones that discontinued showed no improvement in their clinical status," Dr Grande said.

She noted that concerns about adverse effects prevent many clinicians from trying oral ketamine in the management of chronic pain, but she has found that starting slowly at a low dose is the key to tolerability.

"The concern of side effects is enough to scare many clinicians away," she said. "They see a couple of people with nausea or a variety of

different side effects and they don't want to try it, but I have seen that if you start patients at an undetectably low dose and increase it slowly, they start noticing an improvement in their quality of life without side effects."

Dr Grande said she started out hoping that oral ketamine would provide a means for getting patients off of opiates completely.

"It doesn't seem to have accomplished that for most people," she said "There are some who got off opiates completely. If they're really motivated to do so this is a tool they can use, but otherwise it just provides an improved quality of life using the opiates they're already on."

Although there is a history of drug abuse with ketamine, Dr Grande noted that she hasn't seen that with her clinical experience.

"I don't see abuse tendencies in those using it therapeutically for depression and pain."

A growing body of research has been focusing on ketamine, an NMDA receptor antagonist, as a treatment for severe depression, and with extensive research suggesting a link between depression and chronic pain, Dr Grande said improvement in depression may indeed explain some of ketamine's benefits in patients with chronic pain.

"We know about the NMDA effects and there also is the known analgesic effect on neuropathic pain at the spinal cord level, and I think those are two different mechanisms that may be synergistic in people with chronic pain," she said.

Phantom Limb Pain

A separate study from a different group presented at the APS meeting also suggests a similar synergistic effect of ketamine — this time in the acute pain setting, looking at the use of subanesthetic doses of intravenous ketamine within 30 days of an amputation for the treatment of chronic postamputation phantom limb pain.

The retrospective study evaluated outcomes of patients undergoing limb amputation who received ketamine treatment during hospitalization and initiated within 30 days of limb amputation.

The study is ongoing and early results are inconclusive, but the authors reported that ketamine-related efficacy in improving neuropathic pain was documented in 41% of the 25 patients who received the treatment.

While 61% of patients had recorded adverse effects, 35% were described as very mild, self-limited, and generally well tolerated, first author Kellie Jaremko, MD, PhD, from Thomas Jefferson University, Philadelphia, Pennsylvania, told *Medscape Medical News*.

"Typically side effects become tolerable with slight downward titration while efficacy is maintained," Dr Jaremko said. At least 17% of patients reporting adverse effects could not conclusively say whether they were due to other medications, such as opioids, which almost all patients received, she added.

Senior author on the paper is Eugene R. Viscusi, MD, professor of anesthesiology, director, Acute Pain Management, Department of Anesthesiology, Sidney Kimmel Medical College, also at Thomas Jefferson University.

The majority of adverse effects occurred in the first 2 days after initiation of infusion, and all resolved within 12 to 24 hours. One patient experienced adverse effects, including hallucinations and confusion, that were severe enough to require ketamine discontinuation. There were no cardiovascular, hepatic, or neurologic adverse effects.

"This suggests that at the subanesthetic doses used, in an average of less than 25 mg/hour or 0.3 mg/kg per hour, ketamine is generally a well-tolerated treatment," Dr Jaremko said.

The effect of ketamine analgesia on blocking upregulation of neuropathic pain signalling at the spinal cord level could "decrease the central sensitization purported to underlie phantom limb pain," she said, adding that the effects on depression could also be of benefit.

"The newer work with ketamine in depression is intriguing, and we cannot discount that this may contribute to subjective decreases in pain during the postoperative period, but more research is needed to elucidate this possible effect in acute pain," Dr Jaremko said.

Other benefits of an opioid-sparing pain regimen for amputation include a decreased risk for respiratory depression, and although the ketamine treatment is better tolerated than opioids, it is easier to mitigate adverse effects by decreasing the dose.

Importantly, there are currently no highly effective treatments for management of phantom pain, Dr Jaremko said.

"The benefits of a ketamine infusion are better pain control leading to greater engagement in the active recovery process. This may decrease hospital stays and decrease chronic phantom limb pain, but this still needs to be explored.

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