Low-Dose Ketamine for Acute Pain Management
A Timely Nudge Toward Multimodal Analgesia

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The Consensus Guidelines on the Use of Intravenous Ketamine for Acute Pain Management, drawn up by an expert panel from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists, could hardly be published at a more fitting moment. The guidelines come as we struggle to implement multimodal analgesic regimens and, at least in the United States, face a complex and unprecedented opioid crisis.

How did we get to this difficult impasse—and why do we struggle with pain management in the first place? At first glance, one might think that acute pain management after surgery is easy. We largely know which procedures are painful, we have tools to help identify patients who are likely to experience excessive postsurgical pain, and we have at our disposal a wide array of therapeutic modalities across different steps of the classic World Health Organization step ladder, from oral acetaminophen to invasive procedures such as neuraxial anesthesia and nerve blocks. So theoretically, we could allow the patient to be virtually pain-free during the perioperative period after most types of surgery.

As one delves further in to the science, however, one learns that the benefits of these modalities are linked to inherent risks and limitations related to the patient, procedure, and institution. We often do not use the most effective modality to treat patients, but the one we consider most appropriate after weighing risks and benefits. For example, even though strong evidence tells us that a combination of femoral and sciatic nerve blocks is the most effective modality to treat acute pain after knee arthroplasty, this practice has been abandoned in many institutions; as more emphasis is placed on early mobilization (including the drive to decrease the incidence of deep venous thrombosis and pneumonia), avoidance of falls, and early discharge from hospitals, many hospitals now favor the use of local infiltration analgesia and/or adductor canal blocks for patients undergoing total knee replacements. In some cases, we accept more pain knowing that other treatment priorities supersede optimal pain management.

This notwithstanding, the literature on perioperative pain management is still extensive, and thousands of articles have been published on drugs, techniques, and overall strategies. One would assume that with all the knowledge available, despite the limitations outlined above, broadly based multimodal analgesic regimens would be implemented worldwide, and pain scores after surgery would asymptotically approach zero over time. The opposite is true, however. Pain scores (with all their limitations) reported in the literature remain high, even after surgeries that are considered to be minor, a phenomenon observed across age groups and continents. Standardization of analgesic protocols has been advocated, but most perioperative patients in the United States and many other countries still receive a nonmultimodal, nonregional, opioid-based analgesic regimen.

In the first part of 2018, health care providers in the United States have been further affected by an opioid crisis that has 2 distinct facets. First, too many people are taking prescription opioids chronically, and some of those individuals move on to use related street drugs, such as fentanyl, acetyl-fentanyl, carfentanil, and mixtures of heroin and fentanyl. Sadly, all too many addicts overdose and die. Current estimates for annual deaths are in excess of 60,000, meaning that more Americans die every year of drug overdose than American soldiers died during the entire Vietnam War. In the United States today, 75% of people who abuse heroin transitioned from long-term use of prescription opioids. Sun and colleagues identified several surgeries and patient collectives especially prone to chronic opioid use. The prototypical at-risk patient in the analysis by Sun et al was an elderly male with a previous history of substance abuse or depression about to undergo total knee arthroplasty. The challenge for the future is to balance adequate pain therapy, judicious opioid use, and controlled tapering of postoperative opioids to prevent long-term dependence.

The second facet of the opioid crisis is that starting in the latter months of 2017 US hospitals have been faced with a shortage of parenteral opioids for use in the acute perioperative setting. Recent
regulatory changes and corporate reorganizations led to an uncoordinated downturn in production that led to a severe shortage of parenteral opioids, especially fentanyl; the current shortage is projected to last into the second half of 2018. In many institutions, anesthesiologists and surgeons have developed opioid reduction protocols that have made it possible to provide pain control with fewer opioids without adversely affecting patient care.

The confluence of these 2 opioid-related crises has brought new awareness and focus to treating acute postoperative pain. There is now significant societal pressure to reduce opioid use both inside the hospital and in the outpatient setting.

Thus, the Consensus Guidelines on the Use of Intravenous Ketamine for Acute Pain Management, drawn up by an expert panel from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists,1 are appearing at a time when we desperately need to find viable alternatives to the exclusive use of opioid analgesics.

Ketamine is one of the older drugs used by anesthesiologists. It has been in clinical use for more than 50 years. In recent years, there has been a resurgence in the use of ketamine outside the operating room. It has shown promise for the treatment of chronic pain, depression, and complex regional pain syndrome. Perioperatively, ketamine has become one of the first-line agents when postoperative patients are not responding to increasing doses of opioids or have contraindications to high doses of opioids, and regional anesthesia is not a preferred option, but the evidence on how and when to use it has remained ambiguous. Ketamine has a multitude of different pharmacologic actions including antagonism at the N-methyl-D-aspartate receptor, potentiation of γ-aminobutyric acid-mediated central nervous system inhibition, binding to μ-, δ-, and κ-opioid receptors, increasing norepinephrine, dopamine, and serotonin levels, and interactions with cholinergic receptors, the purinergic system, calcium channels, and potassium channels. Finally, ketamine can block sodium channels much like local anesthetics.21 Clinically, ketamine acts as an analgesic, dissociative anesthetic, bronchodilator, anti-inflammatory drug, neuroprotective agent, and antidepressant.22 Adverse effects are very frequently observed at higher doses,23 but low-dose application is generally well tolerated and, when used in combination with opioids, results in opioid-sparing effects coupled with a reduction in opioid-related adverse effects.24 In the long term, ketamine may even help to prevent chronic pain,25 but this concept is still debated.

The new guidelines appearing in this issue of Regional Anesthesia and Pain Medicine recommend that subanesthetic ketamine infusions should be considered for patients undergoing large painful procedures, patients who are opioid dependent, opioid-tolerant patients with chronic pain who have an acute exacerbation, and patients at risk of adverse effects from high doses of opioids such as patients with obstructive sleep apnea. Moderate evidence supports the use of low-dose ketamine as a bolus followed by an infusion for providing perioperative analgesia, optimally in conjunction with an opioid administered by patient-controlled analgesia. The contraindications to use of ketamine are like those for the patient with chronic pain: use should be avoided in patients with uncontrolled cardiovascular disease, pregnancy, and psychosis. Ketamine should be used with caution in patients with moderate liver disease and avoided in patients with cirrhosis. The use of nonparenteral ketamine may be beneficial in some settings, but more studies of high quality are needed to better weigh risks and benefits.1

The dose and mode of ketamine use suggested in the present guidelines differ from those used in the recent high-profile PODCAST trial, which used a single large bolus of ketamine before incision in older patients and found a higher incidence of postoperative delirium with no benefit in terms of pain.23 In contrast, studies with a much smaller sample size where low-dose ketamine was added to opioids postoperatively show only a small decrease in pain intensity but substantial reduction in opioids and opioid-related adverse effects such as postoperative nausea and vomiting.26,27

Use of low-dose ketamine may well be a valuable strategy to help with both aspects of the current opioid crisis. The authors themselves point out that ketamine may have considerable value in reducing perioperative opioid doses, and use of less opioid may reduce long-term opioid use after surgery. There is no evidence at present to support the latter notion, and trials are urgently needed that evaluate whether the low-dose administration of ketamine or other opioid-sparing strategies have the potential to both improve short-term outcomes and decrease the number of people who transition to long-term opioid use or dependency. As to the present-day parenteral opioid shortage, ketamine has the potential to become a central pillar in both reducing our reliance on parenteral opioids and accelerating the transition to more widespread use of multimodal perioperative analgesia.

The authors are to be commended for their substantive efforts to summarize the literature addressing the use of ketamine as an analgesic. The committee has highlighted the deficiencies in the published research and the lack of more robust studies, specifically, the lack of available trials to define the efficacy of ketamine in specific surgical settings and specific patient populations. Another point in urgent need of clarification is the mode of delivery and dose of ketamine in the perioperative setting. The authors recommend a maximum ketamine dose of 0.35 mg/kg for bolus application and 1 mg/kg per hour for continuous infusion. However, as the authors identify in the discussion, many studies achieved a substantial opioid reduction at much lower doses. Ketamine should probably be titrated to the lowest effective dose, which may be as low as 0.15 mg/kg per hour (2.5 μg/kg per minute).28 As we move toward precision treatment of patients, future studies will need to establish the indications and dosing for ketamine based on the specific procedure being performed and take into account individual patient characteristics, for example, genetic risk factors for acute and chronic pain.

Ketamine is reemerging as a useful tool in the field of acute perioperative pain medicine, and the risk-benefit ratio for low-dose ketamine appears to be favorable in most patients. The sensible and balanced guidelines presented in this issue of Regional Anesthesia and Pain Medicine provide clinicians with a thoughtful blueprint on how to use the drug safely to the benefit of patients.

REFERENCES


