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SOCIETY FOR NEUROSCIENCE IN ANESTHESIOLOGY AND CRITICAL CARE

ARTICLE OF THE MONTH

Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

Murphy G, Avram M, Greenberg S, et al.
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Welcome to another session of Article of the Month, August 2021. This month we discuss Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients, commentary by Dr. Paul D Mongan. Dr. Mongan is a Professor of Anesthesiology at the University of Florida in Jacksonville. He began his career in neuroanesthesia and research when he learned to setup and operate a Nicolet Compact Four (Nicolet Instruments, Madison, Wis.) for intraoperative neuromonitoring in the late 1980's. He is the author of numerous manuscripts and a co-editor of the textbook "A Practical Approach to Neuroanesthesia". Dr. Mongan's current research efforts are focused on outcomes after mechanical thrombectomy and the effects of low dose volatile anesthetics and transcranial motor evoked potentials.

As always, we encourage our readers' input on this topic on the SNACC **Twitter** feed, or on **Facebook**.

- Amie Hoefnagel, MD, Oana Maties, MD, Shilpa Rao, MD, and Nina Schloemerkemper, MD.

Commentary

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Patients undergoing spinal fusion surgery are at high risk for moderate-to-severe postoperative pain and associated opioid-related complications. In a previous evaluation, Murphy et al 2017 showed that methadone reduces the requirement for post-operative narcotics with improved pain scores and limited side effects when compared to intravenous hydromorphone in patients undergoing 1-2 level spinal fusions.[1] The primary hypothesis of Murphy et al. in this current article was to determine if hydromorphone use was decreased on the first postoperative day in patients administered methadone/ketamine compared to methadone for 1-2 level spinal fusion surgery.[2] The rationale behind this current

project is that ketamine and methadone, N-methyl-D-aspartate (NMDA) receptor antagonists, have been effective components of multimodal anesthetic protocols. Both have been shown to be effective in improving pain scores and reducing opioid consumption after spine surgery and the combination may have additive benefits.

PROTOCOL AND RESULTS

127 patients with low self-reported preoperative opioid use underwent spinal fusion (>92% lumbar and sacral fusions), using propofol, sevoflurane (1.0%), and remifentanil infusions (0.1 μg-kg−1-min−1) supplemented with low doses of fentanyl and hydromorphone at the discretion of the assigned anesthesia team. 61 patients were randomized to receive intravenous methadone (0.2 mg/kg, maximum of 20 mg) and another 66 patients received methadone supplemented with ketamine (intraoperative 0.3 μg-kg−1-min−1 and 0.1 μg-kg−1-min−1 in the recovery room through 48 hours).

The major postoperative differences in the methadone/ketamine group were a 10-minute delay in hydromorphone administration in the PACU (median 20 vs 30 minutes) and lower 24-hour (2.0 vs 4.6 mg) and 72-hour dosing (2.7 vs 5.8) along with a 45% reduction oral hydrocodone 5 mg/acetaminophen 325 mg tablets at 72 hours.

Using a target pain score of 3 (0-10 numeric pain scale) at rest, cough, and movement every 15 minutes in recovery and then twice daily, both groups reported acceptable mean pain scores (3-5), with the methadone/ketamine group reporting lower pain scores at all time intervals during the first 3 postoperative days (difference 1-2). Both groups related high satisfaction with their pain management. In addition, the overall incidence of medical complications and ketamine/opioid related side effects was low (<4%) and not different between the groups. There was no difference in length of stay.

COMMENTS AND ANALYSIS

In this clinical trial, spinal surgical patients randomized to receive intraoperative methadone (0.2 mg/kg, maximum of 20 mg) with a low dose perioperative ketamine infusion required significantly less intravenous and oral opioid pain medications during the hospital stay, had slightly lower pain scores and similar satisfaction in comparison to methadone alone.[2] The associated timeline from clinical trials registration (July 2016) to manuscript submission (August 2020) highlights the extended timeline from protocol completion, enrollment, data collection, and analysis. In essence, randomized trials are a huge commitment for investigators and organizations and the authors are commended for the high-quality design, management, and data collection in this evaluation.

This study in concert with their previous investigation indicates that postoperative narcotic consumption is limited, side effects are low and patient satisfaction with pain management is high when single-dose methadone is a part of the pain management strategy.[1] The use of intravenous methadone during lumbosacral spine fusion surgery is superior to intermediate-acting narcotics (hydromorphone) to facilitate high-quality postoperative pain management.

The primary targets of pain management strategies are to achieve good pain control at rest and with movement, provide for a rapid transition to oral therapies, reduce infusions and the use of patient-controlled analgesia devices to facilitate early ambulation and physical therapy. Another important factor is reducing the number of nurse interactions for intravenous narcotics and prn medications. Combined, these targets strive for the overarching goals of reducing/minimizing side effects, reducing cost, providing high patient satisfaction, and improving length of stay. There was a measurable reduction in post-operative narcotics with the addition of a low-dose ketamine infusion for 48 hours. However, the clinical relevance of this difference is debatable as it maintained an infusion therapy, did not reduce side effects, nor improve patient satisfaction, or reduce length of stay. However, the methadone/ketamine group had an estimated decrease of 15-20 nursing interventions for pain management over the course of the hospital stay.

No well-controlled design is perfect and other effective intra-operative and scheduled multi-modal therapies (acetaminophen, low dose nonsteroidal anti-inflammatory drugs (NSAIDS), gabapentinoids, and dexamethasone) were not addressed in this study.[3-6] NSAIDS, while controversial, may play a role in optimizing pain management after spine surgery and a previous meta-analysis showed no association with short term low dose NSAID administration and nonunion.[4, 5] In contrast, the current study avoided the use of scheduled multimodal therapies (i.e 3-4 nursing interventions/day)

Other modalities may also have benefits. In a review of low to moderate quality studies for spinal surgery, liposomal encapsulated bupivacaine improved pain scores, reduced morphine equivalents, and reduced length of stay.[7] Future high-quality studies evaluating methadone in conjunction with liposomal encapsulated bupivacaine and other multimodal therapies are warranted to determine if similar narcotic reductions and satisfaction can be achieved with low side effects and reduced cost.

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