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Intraoperative Methadone Improves Postoperative Pain Control in Patients Undergoing Complex Spine Surgery

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BACKGROUND: Patients undergoing complex spine surgery frequently experience severe pain in the postoperative period. The combined opiate receptor agonist/*N*-methyl-D-aspartate receptor antagonist methadone may be an optimal drug for these patients given the probable involvement of *N*-methyl-D-aspartate systems in the mechanism of opioid tolerance and hyperalgesia.
METHODS: Twenty-nine patients undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion were enrolled in this prospective study and randomized to receive either methadone (0.2 mg/kg) before surgical incision or a continuous sufentanil infusion of 0.25 μg/kg/h after a load of 0.75 μg/kg. Postoperative analgesia was provided using IV opioids by patient-controlled analgesia. Patients were assessed with respect to pain scores (visual analog scale from 0 to 10), cumulative opioid requirement, and side effects at 24, 48, and 72 hours after surgery.
RESULTS: Demographic data, duration, and type of surgery were comparable between the groups. Methadone reduced postoperative opioid requirement by approximately 50% at 48 hours (sufentanil versus methadone group, median [25%/75% interquartile range]: 63 mg [27.3/86.1] vs 25 mg [16.5/31.5] morphine equivalents, $P = 0.023$; and 72 hours: 34 mg [19.9/91.5] vs 15 mg [8.8/27.8] morphine equivalents, $P = 0.024$) after surgery. In addition, pain scores were lower by approximately 50% in the methadone group at 48 hours after surgery (sufentanil versus methadone group [mean ± SD] 4.8 ± 2.4 vs 2.8 ± 2.0, $P = 0.026$). The incidence of side effects was comparable in both groups.
CONCLUSION: Perioperative treatment with a single bolus of methadone improves postoperative pain control for patients undergoing complex spine surgery. (Anesth Analg 2011;112:218–23)

Patients undergoing major spine surgery experience severe pain in the postoperative period, which may increase morbidity and the incidence of complications, as well as prolong postoperative rehabilitation. In addition, postoperative pain itself is a risk factor for development of chronic pain syndromes.[1,2]

Many anesthesiologists use a sufentanil infusion in combination with propofol as part of a total IV anesthetic for patients undergoing complex spine surgery wherein neurophysiologic monitoring is frequently used. Compared with remifentanil,[3] sufentanil improves immediate postoperative pain control without a significant delay in tracheal extubation; however, because patients undergoing complex spine surgery continue to experience pain postoperatively, a long-acting opioid, such as methadone, has been suggested as a safe alternative to a continuous infusion of sufentanil.[4]

Methadone, often used as a replacement opioid in therapy for opiate dependency, is also frequently prescribed for patients with chronic pain. Despite the potential benefit of this long-lasting medication, it is not widely used in the perioperative setting. The potential benefits of methadone include a decreased need for patient-controlled analgesia (PCA) because of its long duration of action. Potential problems include difficulty in managing side effects, including sedation, respiratory depression, nausea, and vomiting, which may be increased when using a narcotic that has a long duration.

We designed this prospective, randomized, single-blinded study to explore the efficacy and examine the side effects of a single intraoperative dose of methadone compared with continuous sufentanil infusion in patients undergoing major lumbar spinal surgery.

METHODS

After approval from the IRB, and after obtaining written informed consent, 30 adult patients (aged 18 to 75 years) undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion were included in the study. Exclusion criteria included preoperative methadone therapy; morbid obesity with a body mass index >36.0 kg/m^2; patients with chronic renal failure defined by serum creatinine >2.0 mg/dL; or liver failure defined as a history of cirrhosis or fulminant hepatic failure. Patients with preoperative alcohol or drug abuse, patients with a history of

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myocardial infarction or heart failure, and patients with ASA physical status III (except patients with a history of restrictive lung disease secondary to severe scoliosis) or more were also not included in the study.

Randomization was accomplished using a computer-generated list. The research coordinator was unblinded to group assignment and informed the anesthesia team which group the patients were randomized into. The patient, surgeon, and postoperative care team were blinded to group assignment.

Before surgery, patients were asked to rate their pain using a visual analog scale from 1 to 10 by a member of the research team. In addition, information on preoperative opioid consumption was collected.

All patients received 2 mg midazolam IV before the induction of general anesthesia. General anesthesia was induced with propofol 1.5 to 3.0 mg/kg IV. Endotracheal intubation was facilitated using rocuronium bromide or succinylcholine. According to the randomization plan, patients received either an initial loading dose of 0.75 μg/kg sufentanil before surgical incision followed by sufentanil infusion with 0.25 μg/kg/h or methadone 0.2 mg/kg subsequent to intubation. Anesthesia was maintained with propofol 50 to 150 μg/kg/min with the dose continuously adjusted to achieve a target bispectral index level of 40 to 50.

In both the methadone and sufentanil groups, "inadequate anesthesia" (hypertension, tachycardia, patient movement, etc.) was treated with a sufentanil bolus of 0.1 μg/kg IV every 2.5 minutes at the discretion of the attending anesthesiologist. Normothermia was maintained with forced-air warming.

In the sufentanil group, the sufentanil infusion was discontinued with closing of the surgical incision. At the discretion of the attending anesthesiologist, patients were either tracheally extubated and observed at the postanesthesia care unit or stabilized in the intensive care unit and extubated later. In the intensive care unit, all patients were managed so as to facilitate extubation as rapidly as possible. Opioids were never used to sedate intubated patients. Sedation, when necessary, was provided with propofol and/or midazolam.

Postoperative analgesia in all patients included a PCA pump. At the discretion of the attending neurosurgeon, patients received fentanyl, morphine, or hydromorphone for PCA pain control. Patients had been informed at the preanesthetic visit that additional analgesia would be available postoperatively when it was required and they would have the choice of IV or oral supplements. All the opioids used were converted to morphine equivalents for analysis.[5,6]

Postoperatively, patients were asked to rate their pain using a visual analog scale from 1 to 10 by a blinded staff member. Care was taken to assure that patients were not assessed immediately after painful activity. The cumulative opioid requirement at 24, 48, and 72 hours after surgery and the time of the first dose of pain medication were recorded. In addition, complications such as the incidence of hypotension (defined as mean arterial blood pressure <50 mm Hg), the need for vasopressors, the incidence of respiratory depression (defined as a respiratory rate <8 breaths per minute, respiratory arrest, or the need for naloxone), the incidence of hypoxemia or desaturation (defined as oxygen saturation [Sao_2] <90% or the need for a supplemental oxygen to maintain Sao_2 >96%), the incidence of cardiac arrhythmias, myocardial infarction, and the incidence of nausea and vomiting including the treatment were also recorded.

Table 1. Demographic Data

	Sufentanil group (n = 16)	Methadone group (n = 13)	P
Age (y)	53.1 ± 15.0	62.9 ± 9.5	0.051
Weight (kg)	79.2 ± 15.60	73.6 ± 16.18	0.351
Height (cm)	168 ± 10.1	167 ± 11.1	0.775
Body mass index (kg/m^2)	28.1 ± 4.7	26.3 ± 4.6	0.323
Sex (male/female)	6/7	5/11	0.466
ASA physical status (I/II)	0/16	1/12	0.448
Preoperative Opioid Consumption (mg ME)	7.5 (0.0/21.6)	8.0 (0.0/16.6)	0.771

Data are presented as mean ± SD or median (25%/75% interquartile range).
ASA = American Society of Anesthesiologists; ME = morphine equivalents.

Statistical Analysis

Methadone has not been specifically studied in a large population of patients undergoing complex spine surgery, which makes a power or sample-size analysis difficult to perform. To properly power this study, we first conducted a retrospective review of patients undergoing spine surgery using a sufentanil-based technique at our institution. This review revealed a mean morphine consumption of 24 mg in the first 24 hours, with an SD of 6.5 mg. Thus, with an α of 0.05, we estimated that this study had >80% power to detect a 30% difference in the postoperative consumption of morphine if 30 patients would be enrolled between the 2 groups.

Differences between groups were compared using the unpaired Student t test or Mann-Whitney U test as indicated. Incidences of side effects were compared using the χ^2 test or Fisher exact test as indicated. Data are expressed as mean ± SD or median (25%/75% interquartile range). P <0.05 was considered to be statistically significant. Computerized statistical analysis was performed using SigmaStat (Systat Software, Chicago, IL).

RESULTS

One of the 30 patients was withdrawn before dosing of the study drug because of a change in the planned surgical procedure. Therefore, 16 patients were randomized to the sufentanil group and 13 to the methadone group.

As shown in Table 1, demographic data were similar with respect to age, sex, body weight and height, body mass index, and ASA classification. Preoperative opioid usage was not significantly different between the 2 groups (sufentanil versus methadone group, median [25%/75% interquartile range]: 7.5 mg [0.0/21.6] vs 8.0 mg [0.0/16.6] morphine equivalents, P = 0.771). In addition, patients in both groups reported comparable and not statistically different pain scores before surgery (sufentanil versus

Table 2. Perioperative Course

	Sufentanil group (n = 16)	Methadone group (n = 13)	P
Length of surgery (min)	329 (283–475)	285 (248–467.5)	0.313
Time to extubation (min)	11.5 (5.0–33.0)	15.0 (13.5–18.25)	0.582
Estimated blood loss (mL)	675 (400–1175)	800 (500–1212.5)	0.428
Crystalloids intraoperatively (mL)	4000 (3450–4700)	4000 (3175–4975)	0.809
Colloids intraoperatively (mL)	250 (0–625)	500 (0–625)	0.456
Cell-saver blood (mL)	75 (0–409)	323 (105–418)	0.332
Packed red blood cells (units)	0 (0.0–0.5)	0 (0.0–2.25)	0.362
Extubated in operating room (number/total)	12/16	11/13	0.525

Data are presented as median (25th–75th interquartile range).

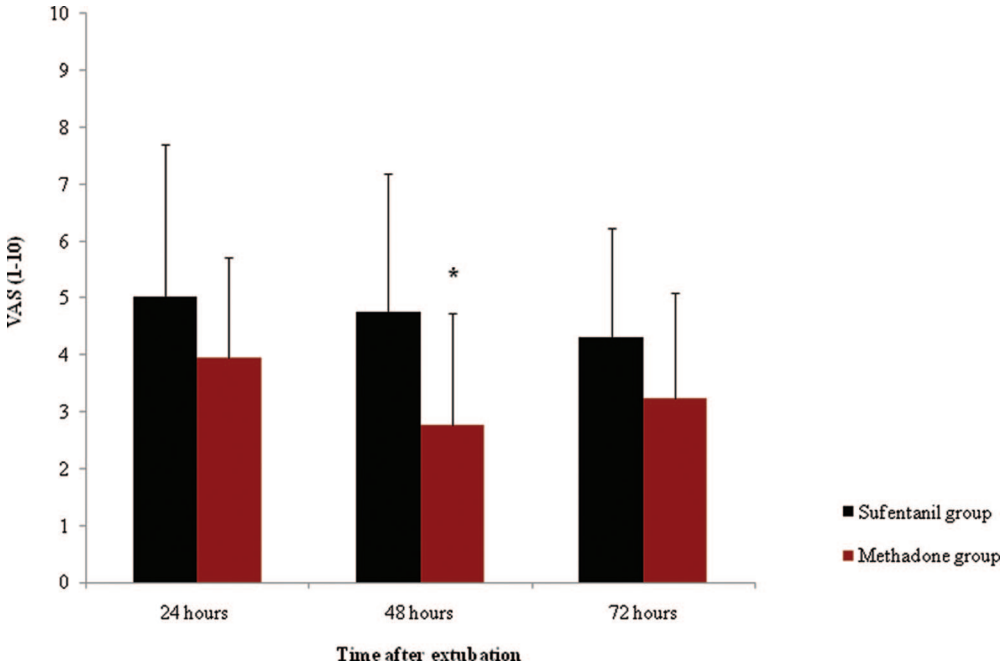

Figure 1. Visual analog scale (VAS) values. Data are presented as mean ± SD. *$P < 0.05$ versus sufentanil group.

methadone group, median [25%/75% interquartile range]: 2.3 [1.0/6.5] vs 1.0 [0.00/6.5], $P = 0.407$).

Patients randomized to sufentanil received 175 ± 56 μg sufentanil total; those in the methadone group received 14.9 ± 3.34 mg methadone. The amount of propofol for induction was not significantly different between the groups (sufentanil versus methadone group [mean ± SD]: 184 ± 36.1 mg vs 163 ± 37.0 mg, $P = 134$), and the total amount of propofol to achieve the target bispectral index value was comparable in both groups (sufentanil versus methadone [mean ± SD]: 2726 ± 831 mg vs 2563 ± 1707 mg, $P = 0.739$). Seven patients in both groups received additional sufentanil boluses with no difference in the total amount of sufentanil (sufentanil versus methadone group, median [25%/75% interquartile range]: 10.0 μg [7.125/17.85] vs 28.0 μg [12.0/35.3] sufentanil, $P = 0.209$).

As shown in Table 2, the length of surgery, time to extubation, estimated blood loss, intraoperative crystalloid and colloid requirements, cell-saver blood, and units of transfused packed red blood cells were comparable.

The time after surgery to first pain medication was not significantly different in both groups (sufentanil versus methadone group [min ± SD]: 57 ± 49.1 minutes vs 89 ± 64.3 minutes, $P = 0.149$). Patients randomized to methadone reported less pain after surgery, which became statistically significant 48 hours after extubation (Fig. 1). In addition, patients in the methadone group had lower postoperative opioid requirements after surgery, which became statistically significant at 48 hours after extubation (sufentanil versus methadone group, median [25%/75% interquartile range]: 63 mg [27.3/86.1] vs 25 mg [16.5/31.5] morphine equivalents, $P = 0.023$) and 72 hours after surgery (sufentanil versus methadone group, median [25%/75% interval]: 34 mg [19.9/91.5] vs 15 mg [8.8/27.8] morphine equivalents, $P = 0.024$) (Fig. 2).

The incidence of side effects in both study arms was similar and is shown in Table 3.

DISCUSSION

Perioperative administration of a single bolus of methadone before surgical incision resulted in a significant reduction of pain scores and reduced requirement of opioids in patients presenting for multilevel complex thoracolumbar spine surgery with instrumentation. To our knowledge,

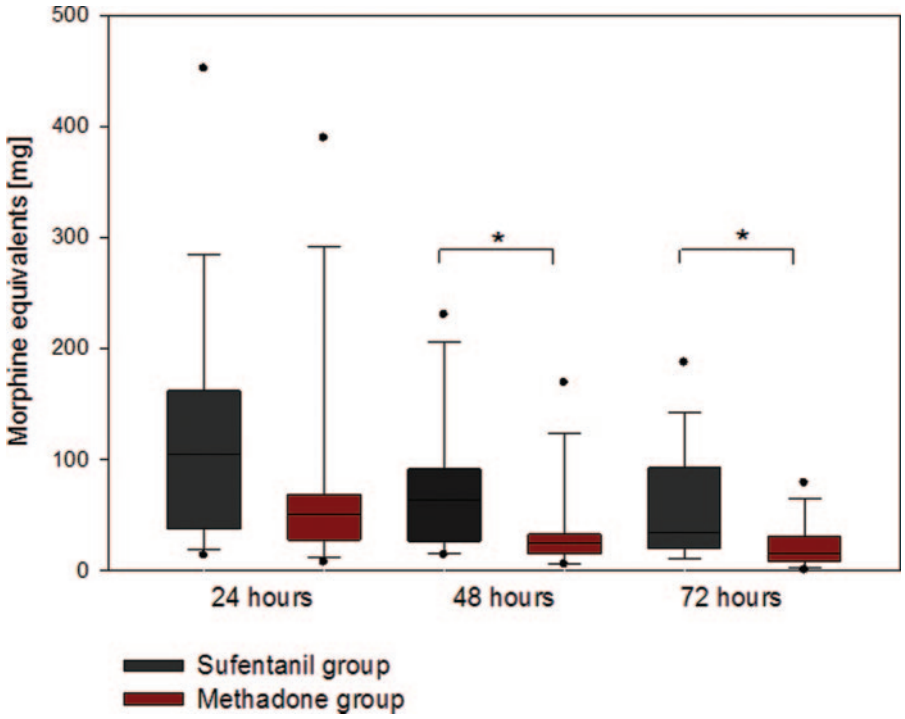

Figure 2. Postoperative opioid requirements in morphine equivalents. The bold line across the box-and-whisker plots is the median, and the upper and lower limits of the box are the 25th and 75th percentiles, respectively. *$P < 0.05$ versus sufentanil group.

Table 3. Reported Side Effects: Sufentanil versus Methadone Group (Number of Patients)

	DOS	POD1	POD2	POD3	At any time	P*
Hypotension	1 vs 0	2 vs 0	0 vs 0	0 vs 0	2 vs 0	0.187
Respiratory depression	0 vs 0	0 vs 0	1 vs 0	0 vs 0	1 vs 0	0.360
Hypoxemia	2 vs 2	1 vs 2	3 vs 1	2 vs 3	3 vs 3	0.775
Arrhythmia	0 vs 0	0 vs 0	0 vs 0	1 vs 0	1 vs 0	0.360
Nausea	4 vs 4	4 vs 3	3 vs 1	2 vs 0	4 vs 4	0.730
Vomiting	2 vs 0	3 vs 1	0 vs 1	0 vs 0	3 vs 1	0.390

* *P* value comparing patients that experienced each complication at any time during their hospitalization.
DOS = day of surgery; POD1 = first postoperative day; POD2 = second postoperative day; POD3 = third postoperative day.

this is the first prospective, randomized study using methadone in this patient population.

Perioperative analgesia remains a major challenge for physicians who care for patients undergoing complex spine surgery. The combination of massive tissue trauma and a patient population, which by definition has significant preoperative pain, complicates optimal postoperative analgesia. Many of the patients control preoperative pain with opioid analgesics, which can result in tolerance and hyperalgesia even before the start of surgery. The exact mechanism underlying the development of acute opioid tolerance and hyperalgesia is unknown but seems to involve activation of dorsal horn *N*-methyl-D-aspartate (NMDA) systems,[7] inactivation of μ-opioid receptors,[8] spinal dynorphin release,[9] and upregulation of the cyclic adenosine monophosphate pathway.[10]

Opioid tolerance can be attenuated with epidural analgesia, which was shown to be a successful approach for pain therapy and resulted in greater patient satisfaction after lumbar spine surgery.[11] Epidural analgesia, although apparently safe and providing superior analgesia, is not widely accepted because of potential difficulty distinguishing an acute change in neurologic function (secondary to an epidural hematoma, for example) from motor blockade by local anesthetics. In addition, many surgeons are concerned that the indwelling epidural catheter may provide a track for bacterial contamination and thus facilitate the development of an infection. Obviously, even small hematomas are an excellent growth medium for bacteria and instrumentation can easily become infected.

The likely involvement of NMDA systems in the mechanism of opioid tolerance and hyperalgesia suggests that the NMDA receptor antagonists may be useful for the treatment of postoperative pain. In addition to its well-characterized opioid receptor agonist effects, methadone is a noncompetitive NMDA antagonist and prevents 5-hydoxytryptamine and norepinephrine reuptake.[12,13] The effect on NMDA receptors contributes to methadone's efficacy in neuropathic pain and mitigation of opioid-induced tolerance.[14] The degree of NMDA receptor antagonism produced by methadone is similar to that of ketamine.[15] However, it was shown that the antinociceptive efficacy of ketamine, in both normal and neuropathic animals, is less than that of drugs acting as agonists on opioid receptors, such as methadone.[16] Methadone is unique in that it is an opioid that can attenuate (or even prevent) opioid tolerance. Despite the

many potential benefits of methadone, there are surprisingly few prospective studies evaluating the use of methadone in the perioperative setting.[4,17]

Methadone has a typical elimination half-life of 15 to 60 hours with a mean of approximately 22 hours. However, metabolism rates vary greatly among individuals, up to a factor of 100, ranging from as few as 4 hours to as many as 130 hours.[18] This variability is apparently attributable to the variable expression of CYP3A4, CYP2B6, and CYP2D6; the effects of enzyme induction; inhibition by other drugs; and environmental factors. This may explain the wide SD 24 hours after surgery in the methadone group. Another explanation for the outliers and wide SD in both groups might be the high incidence of patients with chronic back pain preoperatively who are presenting for spine surgery. In this study, we elected not to exclude patients taking preoperative opioids. This was done because the proportion of patients taking preoperative opioids is high and excluding them from the study would limit its clinical applicability.

One of the more interesting observations in this study is that there was no difference in postoperative opioid consumption during the first 24 hours; patients who received methadone seemed to derive the greatest benefit between 48 and 72 hours. Although there are few studies examining the perioperative use of methadone,[17] we did not expect this result based on the pharmacokinetics of the drug. If the opioid agonist effect of methadone was directly responsible for improved analgesia and decreased opioid requirements, one would have expected the greatest difference during the first 24 hours (as noted above, methadone has a median half-life of 22 hours). Instead, the opposite was observed. This suggests that the primary advantage of methadone might not be its ability to provide analgesia, but rather its ability to attenuate opioid tolerance and hyperalgesia. It is also possible that methadone possesses a preemptive effect; however, this is obviously speculative.

Although these results await confirmation in randomized studies, we submit that methadone may be the ideal analgesic drug for these patients. Unlike gabapentin,[19] methadone requires no special preparation and can be given IV in the operating room immediately after the induction of general anesthesia. Most studies using gabapentin use a large, oral preoperative dose timed 2 to 3 hours before the start of surgery.[19] Furthermore, the duration of analgesia and reduction in postoperative opioid requirements in this study are longer (72 hours) than those observed with gabapentin (24 hours).[19]

One weakness of this study is that the patients, but not the anesthesiologists, were blinded to the study medication; hence, the study was only single blinded. Blinding the surgeons, who were responsible for postoperative pain management, and the postoperative team, which did the pain assessments, to the study medication mitigates this weakness. Nevertheless, confirmation of these results in a larger, double-blind trial would be useful. The large effect size observed in our study indicates that such a trial does not need to be prohibitively large. In addition, it would be interesting to evaluate any potential long-term effects of perioperative methadone on the chronic pain experienced by many of these patients years after surgery.

A potential weakness of this investigation is that patients did not receive equipotent intraoperative opioid doses; patients in the sufentanil group received significantly more intraoperative opioid than patients in the methadone group. Indeed, another potential interpretation of these data is that patients randomized to sufentanil had greater postoperative opioid requirements simply because they have greater postoperative tolerance. Nevertheless, although our results await confirmation in other studies, these data strongly suggest that a clinical approach that avoids an intraoperative sufentanil infusion in favor of a single dose of methadone has superior postoperative results. Furthermore, although this investigation was not powered to detect a difference in postoperative complications, we were not able to demonstrate a difference in intraoperative (Table 2) and postoperative (Table 3) complications with this small sample size.

Another weakness is that the same opioid was not used in the PCA of all patients. Many patients presenting for complex spine surgery had a long experience with various analgesics and had a favored opioid that simply worked better for them. Thus, we thought it in the best interest of patient care to allow patients in both arms of the study to have access to their favored opioid analgesic and use standard conversion ratios to convert all opioid analgesics into morphine equivalents, as stated. Nevertheless, our conclusions are weakened by these inconsistencies in postoperative care.

In summary, perioperative treatment with a single bolus of methadone improves postoperative pain control and reduces opioid requirements in patients undergoing complex spine surgery. The effect of methadone persists for at least 72 hours and is not associated with an increased incidence of adverse events.

RECUSE NOTE

Edward C. Nemergut is the Section Editor of Graduate Medical Education and Transplantation Anesthesiology for the Journal. Marcel E. Durieux is Section Editor of Anesthetic Pre-Clinical Pharmacology for the Journal. The manuscript was handled by Spencer S. Liu, Section Editor of Pain Medicine, and Drs. Nemergut and Durieux were not involved in any way with the editorial process or decision.

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