Clinical Effectiveness and Safety of Intraoperative Methadone in Patients Undergoing Posterior Spinal Fusion Surgery

A Randomized, Double-blinded, Controlled Trial

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ABSTRACT

Background: Patients undergoing spinal fusion surgery often experience severe pain during the first three postoperative days. The aim of this parallel-group randomized trial was to assess the effect of the long-duration opioid methadone on postoperative analgesic requirements, pain scores, and patient satisfaction after complex spine surgery.

Methods: One hundred twenty patients were randomized to receive either methadone 0.2 mg/kg at the start of surgery or hydromorphone 2 mg at surgical closure. Anesthetic care was standardized, and clinicians were blinded to group assignment. The primary outcome was intravenous hydromorphone consumption on postoperative day 1. Pain scores and satisfaction with pain management were measured at postanesthesia care unit admission, 1 and 2 h postadmission, and on the mornings and afternoons of postoperative days 1 to 3.

Results: One hundred fifteen patients were included in the analysis. Median hydromorphone use was reduced in the methadone group not only on postoperative day 1 (4.56 *vs.* 9.90 mg) but also on postoperative days 2 (0.60 *vs.* 3.15 mg) and 3 (0 *vs.* 0.4 mg; all $P < 0.001$). Pain scores at rest, with movement, and with coughing were less in the methadone group at 21 of 27 assessments (all $P = 0.001$ to < 0.0001). Overall satisfaction with pain management was higher in the methadone group than in the hydromorphone group until the morning of postoperative day 3 (all $P = 0.001$ to < 0.0001).

Conclusions: Intraoperative methadone administration reduced postoperative opioid requirements, decreased pain scores, and improved patient satisfaction with pain management. **(Anesthesiology 2017; 126:822-33)**

SEVERE pain in the early postoperative period remains a common yet underestimated and undertreated problem. Despite advances in pain management strategies, many surgical patients continue to suffer from moderate-to-severe pain, particularly during the first three postoperative days (PODs).[1,2] Acute pain after spinal fusion surgery may be particularly difficult for the clinician to manage. Patients undergoing complex spine surgery often present with chronic neuropathic pain and dependence on oral opioid medication. Opioid-induced hyperalgesia and acute opioid tolerance may contribute to postoperative pain that is refractory to treatment with conventional doses of pain medications. Furthermore, chronic neuropathic pain may sensitize patients to painful stimuli after surgery.[3]

Appropriate control of pain is essential for enhancing recovery. Inadequate postoperative analgesia is associated with the development of a variety of adverse events, including cardiac and pulmonary complications, chronic postsurgical pain, decreased patient satisfaction, and increased morbidity and mortality.[4,5] In an analysis of pain intensity following 179 surgical procedures, median pain scores were second highest in patients undergoing posterior spinal fusion.[1] Clinically effective techniques for managing pain after spinal fusion surgery are therefore essential for improving patient outcomes. Several analgesic management strategies have been evaluated in this patient population, including the use of patient-controlled analgesia (PCA)

What We Already Know about This Topic

- Pain after spinal fusion surgery may be particularly acute and difficult to manage
- Methadone is a long-duration opioid that confers postoperative analgesia and opioid-sparing effects

What This Article Tells Us That Is New

- In patients undergoing posterior spinal fusion surgery (averaging two levels), intravenous methadone (0.2 mg/kg) given at induction compared with intravenous hydromorphone (2 mg at surgical closure) resulted in decreased postoperative intravenous and oral opioid requirements and also diminished pain scores and improved patient satisfaction
- There were no differences between the methadone and hydromorphone groups in opioid-related or other adverse events

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opioid administration, intrathecal and epidural analgesia,[2,6] and subanesthetic infusions of ketamine,[7] as well as the use of nonnarcotic analgesic agents, such as gabapentin and intravenous acetaminophen.[8,9] Each of these pain management strategies, however, is associated with additional costs, risks, and side effects.

An alternative approach to reducing pain intensity during the early postoperative period involves the use of a long-duration opioid, such as methadone. Methadone has several unique characteristics that may be advantageous for the patient undergoing multiple-level posterior spinal fusion surgery. It is a potent μ-opioid receptor agonist, with the longest half-life of the clinically used opioids.[10,11] Methadone exerts an inhibitory effect on *N*-methyl-D-aspartate (NMDA) receptors, which are implicated in the development of opioid tolerance, hyperalgesia, and chronic pain.[12–14] Furthermore, methadone inhibits the reuptake of serotonin and norepinephrine; elevation of these monoamines may play a role in antinociception and mood elevation.[15,16] The aim of this parallel-group, randomized, double-blinded, placebo-controlled trial was to assess postoperative analgesic requirements in posterior spinal fusion patients randomized to receive either methadone 0.2 mg/kg at the start of surgery or hydromorphone 2 mg at the conclusion of the procedure. The primary outcome was intravenous hydromorphone consumption on POD 1. Secondary outcomes included pain scores, hemodynamic variables, potential opioid-related complications, and overall patient satisfaction with pain management during the first three PODs. We tested the superiority hypothesis that patients randomized to receive methadone would have reduced analgesic requirements, lower pain scores, and improved quality of recovery during the first three PODs.

Materials and Methods

Study Population and Perioperative Management

The NorthShore University HealthSystem Institutional Review Board (Evanston, Illinois) reviewed and approved this clinical investigation, which was registered at ClinicalTrials.gov (NCT02107339, Principal Investigator Glenn Murphy, Registration Date April 4, 2014; patient enrollment March 3, 2014 to June 6, 2016). The study was conducted at a single tertiary medical center (NorthShore University HealthSystem), and written informed consent was obtained from all subjects. Patients were approached by the study staff and enrolled on the day of surgery. Research assistants and investigators evaluated eligibility, obtained informed consent, and enrolled the participants. The trial was conducted in accordance to the original protocol (full protocol can be obtained by request) and completed after achieving recruitment goals.

A total of 120 patients, ages 18 to 80, presenting for elective posterior lumbar, thoracic, or lumbothoracic spinal fusion surgery were enrolled in this parallel-group randomized, double-blinded, placebo-controlled trial. Exclusion criteria included preoperative chronic renal insufficiency or failure (defined as a serum creatinine more than 2 mg/dl), significant liver disease (cirrhosis or hepatic failure), American Society of Anesthesiologists physical status IV or V, pulmonary disease necessitating home oxygen therapy, preoperative use of methadone or hydromorphone or allergy to either, recent history of opioid or alcohol abuse, or inability to use a PCA device or speak the English language. In addition, any patient judged by the anesthesia care team to potentially require prolonged postoperative intubation was excluded from enrollment.

Using a computer-generated randomization table (simple randomization without restrictions), patients were assigned to one of two groups: a methadone group or a hydromorphone group. Randomization was controlled by the pharmacy, which prepared the study drugs. All care providers and patients were blinded to group assignment. Patients were assigned to receive standard clinical intraoperative doses of either methadone (0.2 mg/kg actual body weight) or hydromorphone (2 mg). Most studies assessing the analgesic clinical efficacy of methadone have used a dose of either 0.2 mg/kg or 20 mg.[10,17–23] Similar doses are frequently administered in clinical practice.[11] An analysis of the previous 20 patients undergoing posterior spinal fusion surgery at our institution revealed that patients received an average dose of 2 mg of hydromorphone intraoperatively. Furthermore, these doses of methadone and hydromorphone appear to be approximately equipotent in patients with chronic and acute pain.[24,25]

Study medications were prepared by the pharmacy in two syringes, one of which contained the study drug while the other contained placebo (saline). Patients randomized to the methadone group received methadone 0.2 mg/kg at induction and saline at the end of the case, and patients randomized to the hydromorphone group received saline at induction and hydromorphone 2 mg at the end of the case, from identical unmarked syringes. The administration of all other anesthetic agents was standardized to reflect usual clinical practices.

Patients were premedicated with intravenous midazolam 2 mg and given oral gabapentin 600 mg. Standard intraoperative monitoring included electrocardiography, an automatic arterial blood pressure cuff, pulse oximetry, capnography, Bispectral Index monitoring (BIS® system, Aspect Medical Systems, USA), and a radial arterial line per clinician judgment. Anesthesia was induced with propofol 1 to 2 mg/kg, lidocaine 50 mg, fentanyl 100 μg, dexamethasone 10 mg, and rocuronium 0.3 to 0.6 mg/kg. Anesthesia was maintained with 1% sevoflurane, remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a propofol infusion titrated to between 50 and 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to achieve a bispectral index value between 40 and 60 and mean arterial pressures within 20% of baseline measurements. Total milligrams of propofol were recorded. Use of additional rocuronium was determined by requirements

for motor-evoked potential monitoring. Hypotension was treated by administration of phenylephrine 80 μg, ephedrine 5 mg, or crystalloids or blood products, as assessed by the anesthesia care team. Hypertension was treated by increasing the infusion rate of propofol. Odansetron 4 mg and intravenous acetaminophen 1,000 mg were given 30 to 60 min before the conclusion of surgery. Neuromuscular blockade was reversed with neostigmine 20 to 50 μg/kg and an appropriate dose of glycopyrrolate. Patients were extubated in the operating room.

On arrival to the postanesthesia care unit (PACU), patients were assessed for pain by nurses per standard protocols. Pain evaluations occurred on PACU arrival and every 15 min thereafter. Patients were administered intravenous hydromorphone 0.25 mg for moderate pain and 0.5 mg for severe pain, and dosing was repeated until pain scores less than or equal to 3 on a scale of 0 to 10 were achieved. The patient was then transitioned to a PCA device that was programmed to deliver intravenous hydromorphone. PACU nurses assessed patients for nausea and vomiting every 15 min, and emetic symptoms were treated. After achieving an Aldrete score of at least 8 out of 10, patients were transferred to surgical wards with continuous pulse oximetry monitoring or to the intensive care unit if more complex monitoring was required.

During PODs 1 to 3, pain was managed with intravenous PCA hydromorphone. Patients were assessed for pain by nurses on the surgical wards every hour per standard protocol. Programming of the PCA device, and the decision when to terminate the use of the device, was at the discretion of the surgical service. Oral opioid therapy was usually initiated on POD 2. Patients were given hydrocodone 10 mg and acetaminophen 325 mg tablets when oral intake was tolerated, and their use was increased on PODs 2 and 3. After the PCA device was discontinued, hydrocodone 10 mg and acetaminophen 325 mg tablets were given at patient request until pain scores less than 4 on a 0 to 10 scale were achieved.

Data Collection

Before surgery, a research assistant questioned patients about daily requirements for oral opioid tablets during the week before surgery, as well as preoperative pain at rest and with coughing and movement on a 0 to 10 verbal analog scale (VAS; 0 = no pain to 10 = worst pain imaginable; this scale was used throughout the investigation). In addition, the level of preoperative sedation was determined on a 0 to 3 scale (0 = fully awake; 1 = mildly sedated, seldom drowsy and easy to awaken; 2 = moderately sedated, often drowsy and easy to awaken; and 3 = severely sedated, somnolent and difficult to awaken). Patients were also questioned about any preexisting nausea, vomiting, or itching. PACU nurses recorded the times required to meet discharge criteria and achieve actual discharge. The total amount of hydromorphone used in the PACU (delivered by nursing staff and the PCA device) was also noted.

At PACU admission, a research assistant recorded pain scores at rest, with coughing, and with movement using a 0 to 10 VAS. Level of sedation, on a 0 to 3 scale, was also assessed as described above. At the same time, patients were evaluated for the following potential opioid-related complications: nausea, vomiting, requirements for antiemetics, itching, hypoventilation (respiratory rate less than 8 breaths/min), and hypoxemia (peripheral oxygen saturation measured by pulse oximetry of less than 90%). Respiratory rate, oxygen saturation, and mean arterial pressure were also recorded, and overall satisfaction with pain management on a 0 to 100 VAS (0 = worst possible to 100 = best possible) was assessed. These same variables were measured again 1 and 2 h after PACU admission, as well as in the mornings (8:00 to 10:00 AM) and late afternoons (3:00 to 4:00 PM) of PODs 1, 2, and 3. The total amount of intravenous hydromorphone and the number of oral hydrocodone tablets were recorded for PODs 1 to 3.

Statistical Analysis

Intravenous PCA hydromorphone is used to control pain during PODs 1 to 3 after complex spine surgery at NorthShore University HealthSystem. In a small study of opioid-tolerant patients undergoing spinal fusion surgery using a standard anesthetic, average hydromorphone consumption in the first 24 h was 27 ± 10 mg.[7] At least a 33% reduction in postoperative hydromorphone consumption was expected in the methadone group. Group sample sizes of 39 and 39 achieve 91% power to detect a difference of 9 between the null hypothesis that both group means are 27 and the alternative hypothesis that the mean of group 2 (methadone group) is 18 with estimated group SDs of 10 and 10 and with a significance level (α) of 0.01 using a two-sided two-sample Student's *t* test. A total of 120 patients were enrolled to ensure complete data collection.

Data for the primary outcome variable, hydromorphone (milligrams) in the first 24 h after the operation, is reported as the median (interquartile range) for both the methadone group and the hydromorphone group. These primary outcome data were compared between groups using the Mann–Whiney U test (StatsDirect, United Kingdom). The median difference and its 95% CI was calculated. The criterion for rejection of the null hypothesis was $P < 0.05$.

Secondary variables that were characterized by nominal data (*e.g.*, opioid-related complications) are summarized as the number of patients in each category and the percentage of all the patients in the group that they represent. These variables were compared between the randomized groups using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test (NCSS, USA). The Miettinen and Nurminen score was used to calculate 99% CIs for differences in percentages where they are reported. Variables that were characterized by ordinal data and nonnormally distributed continuous data (*e.g.*, postoperative analgesic requirements,

level of pain at rest, and overall satisfaction with pain management) are summarized as median and interquartile range. These variables were compared between the randomized groups using the Mann–Whitney U test. Median differences and their 99% CIs were calculated where they are reported. Variables that were characterized by normally distributed continuous data (*e.g.*, extra hydromorphone in the operating room) are summarized as mean and SD. These variables were compared between the randomized groups using the unpaired Student's *t* test (NCSS). Mean differences and their 99% CIs were determined. Because of the large number of comparisons that were made, the criterion for rejection of the null hypothesis was a two-tailed $P < 0.01$ for all between-group comparisons, with that criterion corrected (Bonferroni correction) for multiple comparisons of a variable measured in the randomized groups at multiple times (*e.g.*, postoperative hydromorphone, level of pain at rest, overall satisfaction with pain management, and nausea).

Results

One hundred twenty patients were enrolled in the investigation and randomized to receive the study opioids. Five patients were excluded before study participation (the pharmacy was unable to provide the medications for three subjects and two patients received methadone per clinician preference; four patients were excluded in the hydromorphone group and one patient was excluded in the methadone group). Data were collected and analyzed for 115 subjects (62 patients receiving methadone and 53 given hydromorphone). Figure 1 displays the flow of participants through the study.

The two study groups did not differ strikingly in any preoperative characteristics, including sex, weight, height, American Society of Anesthesiologists physical status, or preexisting medical conditions (appendix A1). The percentage of patients using oral opioid medication preoperatively (53.2% in the methadone group and 52.8% in the hydromorphone group) and the number of hydrocodone 10 mg equivalent tablets used per day by the two groups were similar (appendix A1); therefore, preoperative opioid tolerance was not expected to differ between groups.

Perioperative data are presented in table 1. Type and location of spinal surgery and the number of vertebrae fused did not differ between the two groups. No differences in total anesthesia time or intraoperative doses of propofol or remifentanil were observed between the groups. Extubation times were not prolonged in the methadone group compared to the hydromorphone group. The times required to meet PACU discharge criteria and achieve actual discharge were not influenced by use of intraoperative opioid.

Postoperative PCA hydromorphone requirements were reduced in the methadone group compared to the hydromorphone group not only at POD 1, the primary outcome (4.56 *vs.* 9.9 mg; difference [95% CI], –4.80 [–6.40 to –3.10]; $P < 0.0001$), but also at PODs 2 and 3 (table 2). The total amount of PCA hydromorphone self-administered during the first three PODs was also significantly less in the methadone group. Fewer oral opioid tablets were needed in the methadone group on POD 3 when patients were being transitioned from PCA hydromorphone to hydrocodone 10 mg and acetaminophen 325 mg tablets, and total oral opioid requirements were less in this group.

Median VAS pain scores (on a 0 to 10 scale) reported by patients at rest, with coughing, and with movement were

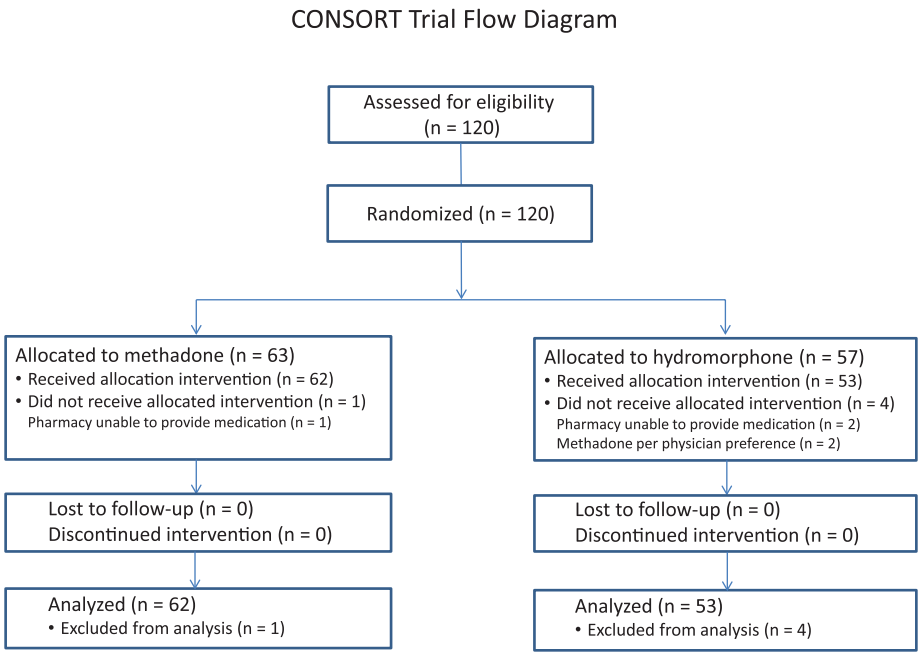

Fig. 1. Patient enrollment and allocation to methadone and hydromorphone groups.

Table 1. Perioperative and Postoperative Data

	Methadone Group	Hydromorphone Group	*P* Value
Operative sites			
Thoracic	9 (14.5%)	4 (7.6%)	0.378
Lumbar	62 (100%)	53 (100%)	—
Sacral	23 (37.1%)	23 (43.4%)	0.620
No. of levels	2 (1–3)	2 (1–2)	0.864
Anesthesia time, min	310 (254–401)	342 (255–410)	0.456
Propofol dose, mg	1,111 (754–1,729)	1,378 (1,108–1,960)	0.021
Fentanyl dose, μg	100 (100–100)	100 (100–100)	0.882
Remifentanil dose, μg	2,311 (1,851–3,117)	2,302 (1,806–3,357)	0.946
Methadone dose, mg	16.7 ± 4.2	0	—
Extra hydromorphone in operating room, n (%)	15 (24.2%)	14 (26.4%)	0.954
Extra hydromorphone in operating room, mg	1 ± 0.6*	0.9 ± 0.6†	0.537
Total hydromorphone in operating room, mg	0 (0–0)	2 (2–2.4)	—
Fluid volume, ml	2,710 ± 843	2,849 ± 954	0.406
Estimated blood loss, ml	350 (250–550)	400 (300–600)	0.499
Erythrocytes, n (%)	4 (6.5%)	3 (5.7%)	0.999
Fresh frozen plasma, n (%)	0 (0%)	0 (0%)	—
Platelets, n (%)	0 (0%)	0 (0%)	—
Urine output, ml	513 (340–800)	350 (200–600)	0.025
Time of tracheal extubation, min	13 (7–18)	12 (9–17)	0.993
Time of first flatus, h	52.5 (40.5–75)‡	46 (36–54)§	0.028
Time of first bowel movement, h	78 (52–97)‖	77 (52–91)#	0.576
Time postanesthesia care unit discharge criteria met, min	93 (78–117)	96 (75–114)**	0.431
Time of postanesthesia care unit discharge, min	114 (100–156)	118 (95–143)††	0.441
Duration of hospitalization, days	4 (3–5)	4 (3–4.75)	0.332

Data are mean ± SD, median (interquartile range), or number of patients (%). Data reported as mean ± SD were compared using the unpaired Student's *t* test, data reported as median (interquartile range) were compared using the Mann–Whitney U test, and data reported as number of patients (%) were compared using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. No *P* value met the criterion for rejection of the null hypothesis. n = 62 in the methadone group and n = 53 in the hydromorphone group, except where indicated.

*n = 15. †n = 14. ‡n = 44. §n = 37. ‖n = 31. #n = 22. **n = 50. ††n = 51.

Table 2. Postoperative Analgesic Requirements

	Methadone Group	Hydromorphone Group	Difference (99% CI)	*P* Value
Hydromorphone, mg				
PACU	1 (0.50–1.60)	1.85 (1–2.35)*	−0.6 (−1.1 to −0.1)	0.001
First 24 h	4.56 (2.30–7.10)	9.90 (6.45–13.20)	−4.80 (−6.90 to −2.60)	< 0.0001
Second 24 h	0.60 (0–2.80)†	3.15 (0.75–8.20)*	−2 (−3.90 to −0.20)	< 0.001
Third 24 h	0 (0–0.05)‡	0.35 (0–3.40)§	−0.125 (−0.60–0)	< 0.001
Total	5.85 (3.10–9.80)	14.60 (9.80–23.30)	−8.20 (−12.10 to −4.50)	< 0.0001
Oral pain tablets				
First 24 h	1 (0–2)	2 (1–3)	−1 (−1 to 0)	0.057
Second 24 h	3 (1–4)†	4 (2–7)*	−2 (−3 to 0)	0.005
Third 24 h	3 (1–5)‡	6 (3–9)§	−3 (−5 to −1)	0.0001
Total	7.5 (4–12)	12 (6–18)	−4 (−8 to −1)	0.001

Data are reported as median (interquartile range) and were compared between groups at the various times using the Mann–Whiney U test. No within-group (*i.e.*, across time) comparisons have been made. Oral pain tablets = hydrocodone 10 mg and acetaminophen 325 mg. n = 62 in the methadone group and n = 53 in the hydromorphone group, except where indicated.

*n = 52. †n = 61. ‡n = 60. §n = 48.

PACU = postanesthesia care unit.

lower in the methadone group compared to the hydromorphone group at all assessment times, except pain at rest in the afternoons of PODs 1, 2, and 3 and pain with coughing in the afternoons of PODs 1 and 3 (table 3). Overall satisfaction with pain management (on a 0 to 100 VAS) was higher in the methadone group from PACU admission through the morning of POD 3.

No patients were intubated overnight due to opioid-induced ventilatory depression. The study groups did not differ in the incidences of nausea, vomiting, requirements for treatment of nausea or vomiting, itching, hypoventilation, or hypoxemic events from PACU admission through the afternoon of POD 3 (appendix A2). Sedation scores, respiratory rates, peripheral oxygen saturation measurements, and mean

Table 3. Levels of Pain at Rest, with Coughing, and with Movement and Overall Satisfaction with Pain Management

	Methadone Group	Hydromorphone Group	Difference (99% CI)	*P* Value
Level of pain at rest				
Preoperative	4 (1–7)	4 (2–6)	0 (–2 to 2)	0.844
At PACU admission	5 (1–7)*	8 (6–10)†	–3 (–5 to –2)	< 0.0001
1 h after admission	4 (3–6)‡	6 (5–9)§	–2 (–4 to –1)	< 0.0001
2 h after admission	4 (2–4)‡	6 (4–7)†	–2 (–4 to –1)	< 0.0001
Postoperative day 1—AM	4 (2–5)	5 (3–8)‖	–2 (–3 to –1)	< 0.001
Postoperative day 1—PM	4 (2–5)	5.5 (3–7.5)#	–1 (–3 to 0)	0.009
Postoperative day 2—AM	4 (2–5)**	6 (3.5–8)#	–2 (–3 to –1)	< 0.001
Postoperative day 2—PM	4 (2–5)††	5 (3–7)§	–1 (–3 to 0)	0.021
Postoperative day 3—AM	4 (2–5)††	5 (3–7)‡‡	–1 (–3 to 0)	0.007
Postoperative day 3—PM	4 (2–6)§§	5 (3–7)‖‖	–1 (–3 to 0)	0.033
Level of pain with coughing				
Preoperative	5 (2–8)	5 (2–8)	0 (–2 to 2)	0.908
At PACU admission	5 (2–7)*	9 (7–10)†	–3 (–5 to –2)	< 0.0001
1 h after admission	5 (3–7)‡	7 (5–9)§	–2 (–4 to –1)	< 0.0001
2 h after admission	4 (2–5)‡	6 (5–8)†	–3 (–4 to –1)	< 0.0001
Postoperative day 1—AM	4 (3–5)**	7 (5–9)§	–2 (–4 to –1)	< 0.0001
Postoperative day 1—PM	5 (3–5.5)**	7 (4–8)‖	–2 (–3 to 0)	0.002
Postoperative day 2—AM	5 (2.5–6)**	8 (5–9)#	–3 (–4 to –1)	< 0.0001
Postoperative day 2—PM	4 (2–6)*	7 (4–8)§	–2 (–4 to –1)	< 0.001
Postoperative day 3—AM	4 (3–5)††	6 (4–8)‡‡	–2 (–3 to –1)	0.0001
Postoperative day 3—PM	5 (3–6)§§	6 (3.58)‖‖	–1 (–3 to 0)	0.052
Level of pain with movement				
Preoperative	8 (6–10)	8 (7–10)	0 (–2 to 1)	0.333
At PACU admission	5 (3–8)*	9 (7–10)†	–3 (–4 to –2)	< 0.0001
1 h after admission	5 (3–7)‡	7 (5–9)§	–2 (–4 to –1)	< 0.0001
2 h after admission	4 (3–5)‡	6 (5–8)†	–3 (–4 to –1)	< 0.0001
Postoperative day 1—AM	5 (4–6)	9 (7–10)‖	–3 (–4 to –2)	< 0.0001
Postoperative day 1—PM	5 (5–7)	8 (5.5–9)#	–2 (–3 to –1)	< 0.001
Postoperative day 2—AM	6 (4–7)**	7 (6–9.5)#	–2 (–3 to –1)	< 0.0001
Postoperative day 2—PM	5 (3–8)††	8 (6–9)§	–2 (–3 to 0)	0.001
Postoperative day 3—AM	5 (3–6)††	7 (6–8)‡‡	–2 (–4 to –1)	< 0.0001
Postoperative day 3—PM	5 (4–6)§§	7 (5–8.5)‖‖	–2 (–3 to 0)	0.001
Overall satisfaction with pain management				
At PACU admission	80 (70–90)##	50 (20–70)***	30 (10–40)	< 0.0001
1 h after admission	80 (70–90)‡	60 (40–80)†	19 (5–30)	< 0.001
2 h after admission	80 (70–90)**	60 (45–77.5)‡‡	20 (10–30)	< 0.0001
Postoperative day 1—AM	92.5 (85–100)	80 (70–90)§	10 (5–20)	< 0.0001
Postoperative day 1—PM	90 (80–100)‡	80 (70–90)‖	10 (0–15)	< 0.001
Postoperative day 2—AM	90 (85–100)††	82.5 (70–90)#	10 (2–15)	< 0.001
Postoperative day 2—PM	90 (85–100)††	80 (75–90)§	10 (5–15)	< 0.0001
Postoperative day 3—AM	95 (90–100)††	90 (77.5–95)‡‡	5 (0–10)	0.001
Postoperative day 3—PM	95 (88–100)§§	85 (70–90)‖‖	10 (0–15)	0.003

Data are reported as median (interquartile range) and were compared between groups at the various times using the Mann–Whiney U test. No within-group (*i.e.*, across time) comparisons have been made. Level of pain scores on a 0–10 scale: 0 = no pain to 10 = worst pain imaginable. Overall satisfaction with pain management on a 0–100 scale: 0= worst possible to 100 = best possible. n = 62 in the methadone group and n = 53 in the hydromorphone group, except where indicated.

*n = 58. †n = 49. ‡n = 61. §n = 50. ‖n = 51. #n = 52. **n = 60. ††n = 59. ‡‡n = 48. §§n = 46. ‖‖n = 40. ##n = 56. ***n = 45.

PACU = postanesthesia care unit.

arterial pressures were also similar in the study groups during this time (appendix A2). Times of first flatus and bowel movement and hospital length of stay did not differ between the two study groups (table 1).

Discussion

Patients undergoing posterior spinal fusion frequently experience severe postoperative pain, particularly during the first three days after surgery.[26] Despite treatment with potent intravenous opioids, pain scores of 7 out of 10 (0 = no pain; 10 = worst pain imaginable) have been reported in the early recovery period after surgery.[1,26] Several interrelated factors contribute to the high pain intensity experienced by patients in the postoperative period. Spinal fusion surgery is an invasive procedure involving removal of lamina, bone grafting, and multilevel instrumentation. In addition, patients

presenting for surgery have preexisting neuropathic pain[27] and are often using preoperative oral opioids, which induce tolerance and activate pain facilitatory systems (hyperalgesia and allodynia).[28] Furthermore, acute postoperative pain is typically treated with intravenous intermediate-duration opioids (hydromorphone and morphine) delivered *via* a PCA device. This mechanism of delivery results in significant fluctuations in serum opioid concentrations, resulting in effects that range from inadequate analgesia to overdosage and respiratory depression.[11] The intraoperative administration of the long-duration opioid methadone may be more clinically effective in attenuating postoperative pain than conventional intermediate-duration opioids in patients undergoing complex spine surgery. In the current investigation, patients in the methadone group required significantly less intravenous and oral opioid medication, reported lower pain scores, and had improved global satisfaction with pain management during the first three PODs, compared to subjects given intraoperative hydromorphone. The use of a long-duration opioid was not associated with an increased risk of adverse opioid-related events.

Methadone is a unique μ- and δ-opioid agonist that has a rapid onset of effect (approximately 5 min) and a long duration of effect when used in larger doses (more than or equal to 20 mg).[11] Gourlay *et al.*[10,19,20] determined that the duration of postoperative pain relief was 19 to 21 h when doses of 20 to 30 mg of methadone were administered in the operating room and PACU. Simulated methadone plasma concentration *versus* time relationships estimate the duration of analgesia after administration of 20 mg methadone is 24 and 36 h after a dose of 30 mg.[11] In addition, methadone is an NMDA receptor antagonist, which may play an important role in the pharmacologic clinical effectiveness of this agent in pain treatment. Methadone has antihyperagesic and antiallodynic properties,[28–30] inhibits the development of tolerance,[28–30] and may be effective in the management of neuropathic pain[7,17,31,32]; these effects appear to be mediated by the ability of methadone to block the NMDA receptor. Finally, certain centrally acting analgesics (tramadol and methadone) have been demonstrated to decrease serotonin and norepinephrine reuptake, which may contribute to postoperative analgesia by influencing the sensorial and affective dimensions of pain processing.[15,16]

Only a few clinical trials have examined the use of methadone in patients undergoing spine surgery. Sharma *et al.*[18] randomized 31 adolescent patients undergoing scoliosis surgery to 0.1, 0.2, or 0.3 mg/kg methadone intraoperatively. The authors observed that postoperative analgesic requirements and pain scores were not reduced by increasing methadone doses. In contrast to these findings, Gottschalk *et al.*[17] observed that spinal surgical patients administered methadone had a 50% reduction in both pain scores and analgesic requirements at 48 h. Similar findings were reported in a study of 10 anterior spinal fusion patients.[20] Reduced pain scores and analgesic requirements were observed in patients undergoing abdominal,[10,19] gynecologic,[22,23] major pediatric,[21] and cardiac[33,34] surgery administered methadone at the beginning of the procedures. Limitations present in most of the previous clinical trials included small study sample sizes, lack of randomization or blinding, no standardization of intraoperative anesthetic and postoperative analgesic management, and absence of a control group.

The total doses of intravenous hydromorphone used in this investigation to control postoperative pain were significantly less in the methadone group compared to the hydromorphone group. Our findings confirm the observations from previous investigations in complex spinal and other major operative procedures that the intraoperative administration of methadone is associated with 30 to 50% reductions in postoperative opioid requirements.[10,17,19,21–23,33,34] Patients were transitioned from intravenous to oral opioids on PODs 2 and 3. Fewer oral opioid tablets were requested by patients in the methadone group, particularly by POD 3. These findings demonstrate that the analgesic clinical effects of methadone persists beyond 48 h and may result in a decreased requirement for oral pain medications after intravenous PCA opioids are discontinued.

Median VAS pain scores (on a 0 to 10 scale) reported by patients in the methadone group were significantly lower at rest, with coughing, and with movement from the time of PACU admission until the afternoon of POD 3. As reported in other clinical trials,[10,19,21–23,32,33] reductions in acute postoperative pain described by patients in the methadone group occurred in association with use of a lower overall dose of intravenous opioid at each assessment period. The unique pharmacokinetic and pharmacodynamic properties of methadone likely accounted for these beneficial effects. In contrast, patients in the hydromorphone group reported higher pain scores and required more postoperative opioid medication. Although patients were able to self-administer intravenous opioids, moderate-to-high pain scores were reported by patients in this group; this observation likely reflects the difficulty in treatment of pain after complex spine surgery with conventional opioids.

A primary concern related to the use of methadone is the potential for prolonged respiratory depression. In the current investigation, no differences between study groups were observed in the incidences of postoperative hypoxemia (peripheral oxygen saturation measured by pulse oximetry less than 90%) or hypoventilation (respiratory rate less than 8 breaths/min). Respiratory rate and peripheral oxygen saturation during the PACU admission and on the first three PODs also did not differ between groups. Furthermore, the level of sedation did not differ between groups at any assessment time. Our findings are consistent with all other previous studies that have established that patients given larger doses of methadone (0.2 to 0.4 mg/kg or 20 to 30 mg) are not at increased risk of clinically significant respiratory depression.[10,19,21–23,33,34]

Pain management strategies that improve postoperative analgesia and decrease opioid requirements may be associated with enhanced recovery. Although subjects receiving intraoperative methadone reported lower postoperative pain scores and required less opioids, PACU and hospital lengths of stay were not reduced in this group. Patient satisfaction with pain management, however, was significantly improved in the patients given methadone compared to those administered hydromorphone. This subjective enhancement of global pain perception in the methadone group was likely secondary to several factors, which include prolonged opioid analgesia, less variability in postoperative plasma opioid concentrations, and increased central nervous system serotonin and norepinephrine levels.[10–16]

There are several limitations to this clinical trial. First, methadone dose–response studies have not been performed in adults undergoing spinal fusion surgery; therefore, the optimal dose that produces sufficient analgesia without inducing respiratory depression has not been determined. Patients were administered 0.2 mg/kg methadone in this investigation, as this reflects one of the most commonly used doses examined in previous studies. However, all patients in the methadone group required additional intravenous hydromorphone postoperatively, and median VAS pain scores of 4 to 5 were reported by subjects, which suggest that higher doses may have been more clinically effective. Based on the findings from this study, some patients in our practice are now administered larger doses of methadone (0.3 to 0.4 mg/kg) intraoperatively. Second, a remifentanil infusion was used intraoperatively to reduce inhalational agent requirements, decrease the probability of patient movement, and attenuate hemodynamic responses to surgical stimuli. Because remifentanil induces the expression of acute opioid tolerance and opioid-induced hyperalgesia in laboratory and clinical studies,[35] the same infusion rate and dose was used in both study groups to minimize the potential effect of this opioid on postoperative pain and analgesic requirements. Third, the two study opioids were given at different times during the surgical procedure. The administration of hydromorphone and methadone simultaneously (*i.e.*, at induction of anesthesia) would have removed the confounding variables of time of opioid administration and the possibility that the methadone group had a preemptive analgesic effect (opioid given at the start of surgery), whereas the hydromorphone group did not (opioid given at the end of surgery). However, in a pilot study and previous investigation (ClinicalTrials.gov NCT01546948, data not published), we determined that patients administered all or the majority of hydromorphone at induction of anesthesia had significant pain in the PACU (likely due to the short [2 h] duration of effect of hydromorphone),[36] while patients given all or the majority of methadone during surgical closure frequently required prolonged postoperative intubation. Fourth, high-risk patients were excluded from enrollment; the effect of perioperative methadone on outcomes is uncertain in this patient population.

In conclusion, patients undergoing posterior spinal fusion surgery randomized to receive intraoperative methadone had significantly reduced postoperative analgesic requirements, improved pain scores, and enhanced perception of pain management, compared to patients administered the traditional intermediate-duration opioid hydromorphone. Dose–response studies are needed to further define the optimal dose of methadone in this patient population with severe postoperative pain.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: dgmurphy2@yahoo.com. Raw data available at: dgmurphy2@yahoo.com.

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Appendix A1. Patient Characteristics

	Methadone Group	Hydromorphone Group
n	62	53
Sex (male)	32 (51.6%)	21 (39.6%)
Age, yr	64.5 (57–71)	60 (45–66)
Weight, kg	83.3 ± 20.8	80.7 ± 22.1
Height, cm	170.2(160–180.3)	167.6(160–172.7)
ASA physical status	2 (2–3)	2 (2–3)
Opioid pain medication before surgery	33 (53.2%)	28 (52.8%)
No. of hydrocodone 10 mg equivalent tablets per day	2 (2–2)*	3 (2–4)†
Smoking history	8 (12.9%)	8 (15.1%)
Drinking history	2 (3.2%)	5 (9.4%)
Steroids last month	12 (19.4%)	13 (24.5%)
History of coronary artery disease	9 (14.5%)	5 (9.4%)
Myocardial infarction	1 (1.6%)	2 (3.8%)
Congestive heart failure	1 (1.6%)	2 (3.8%)
Atrial fibrillation	3 (4.8%)	2 (3.8%)
Hypertension	39 (62.9%)	25 (47.2%)
COPD	1 (1.6%)	4 (7.6%)
Sleep apnea	13 (21%)	5 (9.4%)
Thyroid disease	13 (21%)	5 (9.4%)
NIDDM	12 (19.4%)	8 (15.1%)
IDDM	1 (1.6%)	2 (3.8%)
Cerebrovascular accident	1 (1.6%)	1 (1.9%)
Transient ischemic attack	2 (3.2%)	1 (1.9%)
Peripheral vascular disease	1 (1.6%)	0 (0%)

Data are mean ± SD, median (interquartile range), or number of patients (%). Drinking history indicates alcohol consumption of more than two drinks per day.

*n = 33. †n = 28.

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus.

Appendix A2. Opioid-related Complications: Nausea, Vomiting, Itching, Hypoventilation, Hypoxemia, and Sedation

	Methadone Group	Hydromorphone Group	Difference (99% CI)	*P* Value
Nausea				
Preoperative	1 (1.6%)	5 (9.4%)	−7.8 (−23.4 to 4.2)	0.093
At PACU admission	2 (3.3%)*	1 (2%)†	1.4 (−11.9 to 13.7)	> 0.999
1 h after admission	1 (1.6%)	2 (3.9%)†	−2.3 (−16.4 to 9)	0.588
2 h after admission	0 (0%)	0 (0%)‡	0 (−11.9 to 9.7)	—
Postoperative day 1—AM	18 (29%)	20 (39.2%)†	−10.2 (−32.7 to 12.7)	0.347
Postoperative day 1—PM	17 (27.4%)	11 (21.2%)§	6.3 (−15.2 to 26.6)	0.579
Postoperative day 2—AM	11 (17.7%)‖	14 (26.9%)§	−9.2 (−29.9 to 11.0)	0.364
Postoperative day 2—PM	5 (8.3%)*	12 (24%)#	−15.7 (−35.2 to 2.4)	0.046
Postoperative day 3—AM	7 (11.9%)**	8 (16.7%)††	−4.8 (−24.4 to 13.2)	0.666
Postoperative day 3—PM	6 (13%)‡‡	6 (15%)§§	−2 (−23.7 to 18.5)	0.960
Vomiting				
Preoperative	0 (0%)	1 (1.9%)	−1.9 (−14.3 to 8)	0.461
At PACU admission	0 (0%)‖	0 (0%)†	0 (−11.5 to 9.8)	—
1 h after admission	0 (0%)	0 (0%)†	0 (−11.5 to 9.7)	—
2 h after admission	0 (0%)	0 (0%)‡	0 (−11.9 to 9.7)	—
Postoperative day 1—AM	6 (9.7%)	7 (13.7%)†	−4 (−22.2 to 12.4)	0.708
Postoperative day 1—PM	4 (6.5%)	2 (3.9%)§	2.6 (−11.8 to 16.3)	0.687
Postoperative day 2—AM	0 (0%)‖	1 (1.9%)§	−1.9 (−14.6 to 8.1)	0.460
Postoperative day 2—PM	0 (0%)*	1 (2%)#	−2 (−15.1 to 8.2)	0.455
Postoperative day 3—AM	1 (1.7%)**	0 (0%)††	1.7 (−10.7 to 13)	> 0.999
Postoperative day 3—PM	2 (4.4%)‡‡	0 (0%)§§	4.4 (−10.3 to 19.5)	0.497
Treat nausea and vomiting				
At PACU admission	0 (0%)‖	0 (0%)†	0 (−11.5 to 9.8)	—
1 h after admission	0 (0%)	1 (2%)#	−2 (−15.1 to 7.9)	0.446
2 h after admission	0 (0%)	0 (0%)‡	0 (−11.9 to 9.7)	—
Postoperative day 1—AM	12 (19.4%)	14 (26.9%)§	−7.6 (−28.5 to 12.9)	0.462
Postoperative day 1—PM	7 (11.3%)	8 (15.4%)§	−4.1 (−22.6 to 13)	0.714
Postoperative day 2—AM	8 (13.1%)‖	10 (19.2%)§	−6.1 (−25.5 to 12.2)	0.530
Postoperative day 2—PM	2 (3.3%)*	7 (14%)#	−10.7 (−28.1 to 3.6)	0.076
Postoperative day 3—AM	3 (5.1%)**	4 (8.3%)††	−3.3 (−20 to 11.1)	0.698
Postoperative day 3—PM	2 (4.4%)‡‡	1 (2.5%)§§	1.9 (−14.5 to 17.4)	> 0.999
Itching				
Preoperative	7 (11.3%)	6 (11.3%)	0 (−17.6 to 16.4)	> 0.999
At PACU admission	1 (1.6%)‖	1 (2%)†	−0.3 (−13.4 to 10.9)	> 0.999
1 h after admission	2 (3.2%)	2 (3.9%)†	−0.7 (−14.9 to 11.6)	> 0.999
2 h after admission	0 (0%)	2 (4.1%)‡	−4.1 (−18.4 to 5.9)	0.193
Postoperative day 1—AM	13 (11.3%)	18 (35.3%)†	−14.3 (−35.9 to 7.5)	0.137
Postoperative day 1—PM	16 (25.8%)	16 (30.8%)§	−5 (−26.9 to 16.6)	0.705
Postoperative day 2—AM	16 (26.2%)‖	12 (23.1%)§	3.2 (−18.4 to 23.8)	0.866
Postoperative day 2—PM	14 (23.3%)*	12 (24%)#	−0.7 (−22.3 to 20.1)	0.886
Postoperative day 3—AM	11 (18.6%)**	12 (25%)††	−6.4 (−27.9 to 14.3)	0.576
Postoperative day 3—PM	11 (18.6%)**	6 (13%)‡‡	5.6 (−14.7 to 24.3)	0.613
Hypoventilation (respiratory rate < 8 breaths/min)				
At PACU admission	5 (8.1%)	6 (11.5%)§	−3.5 (−20.8 to 12.1)	0.759
1 h after admission	8 (12.9%)	6 (11.5%)§	1.4 (−16.6 to 18.2)	0.948
2 h after admission	4 (6.5%)	3 (6.1%)‡	0.3 (−15.7 to 14.4)	> 0.999
Postoperative day 1—AM	0 (0%)	0 (0%)§	0 (−11.3 to 9.7)	—
Postoperative day 1—PM	0 (0%)	0 (0%)§	0 (−11.3 to 9.7)	—
Postoperative day 2—AM	0 (0%)‖	0 (0%)§	0 (−11.3 to 9.8)	—
Postoperative day 2—PM	0 (0%)*	0 (0%)#	0 (−11.7 to 10)	—
Postoperative day 3—AM	0 (0%)*	0 (0%)††	0 (−12.1 to 10)	—
Postoperative day 3—PM	0 (0%)‡‡	0 (0%)§§	0 (−14.2 to 12.6)	—

(*Continued*)

Appendix A2. (*Continued*)

	Methadone Group	Hydromorphone Group	Difference (99% CI)	*P* Value
Hypoxemia (Spo_2< 90%)				
At PACU admission	4 (6.5%)	5 (9.6%)§	–3.2 (–19.7 to 11.5)	0.730
1 h after admission	3 (4.8%)	2 (3.9%)§	1 (–13.2 to 14)	> 0.999
2 h after admission	2 (3.2%)	0 (0%)‡	3.2 (–9 to 14.9)	0.502
Postoperative day 1—AM	2 (3.2%)	0 (0%)§	3.2 (–8.4 to 14.9)	0.500
Postoperative day 1—PM	3 (4.8%)	2 (3.9%)§	1 (–13.2 to 14)	> 0.999
Postoperative day 2—AM	1 (1.6%)‖	1 (1.9%)§	–0.3 (–13.1 to 10.9)	> 0.999
Postoperative day 2—PM	1 (1.7%)*	1 (2%)#	–0.3 (–13.6 to 11.1)	> 0.999
Postoperative day 3—AM	0 (0%)*	0 (0%)††	0 (–12.1 to 10)	—
Postoperative day 3—PM	0 (0%)‡‡	0 (0%)§§	0 (–14.2 to 12.6)	—
Sedation (on a 0–3 scale, where 0 = awake)				
At PACU admission	2 (1–2)‖	2 (1–2)†	0 (0–0)	0.796
1 h after admission	1 (1–2)	1 (0–1)†	0 (0–1)	0.143
2 h after admission	1 (0–1)	0 (0–0)‡	0 (–1 to 0)	0.394
Postoperative day 1—AM	0 (0–0)	0 (0–0)†	0 (0–0)	0.775
Postoperative day 1—PM	0 (0–0)	0 (0–0)§	0 (0–0)	0.207
Postoperative day 2—AM	0 (0–0)‖	0 (0–0)§	0 (0–0)	0.598
Postoperative day 2—PM	0 (0–0)*	0 (0–0)#	0 (0–0)	0.482
Postoperative day 3—AM	0 (0–0)**	0 (0–0)††	0 (0–0)	0.430
Postoperative day 3—PM	0 (0–0)‡‡	0 (0–0)§§	0 (0–0)	0.014
Respiratory rate, breaths/min				
At PACU admission	14 (12–16)	15 (13.5–17.5)§	–1 (–2 to 1)	0.158
1 h after admission	14 (12–16)	14 (12–16)§	0 (–2 to 2)	0.900
2 h after admission	14 (12–15)	14 (12–16)‡	0 (–1 to 1)	0.756
Postoperative day 1—AM	18 (16–18)	17 (16–18)§	0 (0–1)	0.259
Postoperative day 1—PM	18 (16–18)	18 (16–18)§	0 (0–1)	0.147
Postoperative day 2—AM	18 (16–18)‖	18 (16–18)§	0 (0–0)	0.969
Postoperative day 2—PM	18 (18–18)*	18 (16–18)#	0 (0–0)	0.962
Postoperative day 3—AM	18 (16–18)*	18 (16–18)††	0 (–1 to 0)	0.229
Postoperative day 3—PM	18 (17–18)‖‖	18 (18–18)§§	0 (0–0)	0.212
Spo_2, %				
At PACU admission	98.5 (97–100)	99 (96.5–100)§	0 (–1 to 1)	0.763
1 h after admission	98 (97–100)	99 (96.5–100)§	0 (–1 to 0)	0.304
2 h after admission	98.5 (98–99)	98 (97–99)‡	0 (0–1)	0.576
Postoperative day 1—AM	98 (96–100)	98 (96–100)§	0 (–2 to 0)	0.258
Postoperative day 1—PM	97 (95–99)	97.5 (95–99)§	0 (–1 to 1)	0.581
Postoperative day 2—AM	96 (95–98)‖	96 (95–97)§	0 (–1 to 1)	0.775
Postoperative day 2—PM	96 (94–97)*	97 (95–98)#	0 (–2 to 1)	0.235
Postoperative day 3—AM	96 (94–98)*	96.5 (95–98)††	0 (–1 to 1)	0.694
Postoperative day 3—PM	96 (95–98)‖‖	97 (95–98)§§	0 (–1 to 1)	0.753
Mean arterial pressure, mmHg				
At PACU admission	87 (74–93)	83 (75–90)§	2 (–5 to 8)	0.484
1 h after admission	80.5 (72–90)	83 (73.5–91.5)§	–2 (–8 to 5)	0.480
2 h after admission	79 (72–90)	79 (73–88)‡	0 (–6 to 6)	0.983
Postoperative day 1—AM	77.5 (70–84)	78 (72.5–85.5)§	–2 (–7 to 4)	0.359
Postoperative day 1—PM	74.5 (70–83)	79.5 (72–86)§	–3 (–8 to 2)	0.112
Postoperative day 2—AM	80 (73–87)‖	81 (75–90)§	–1 (–7 to 4)	0.598
Postoperative day 2—PM	83 (72.5–86.5)*	82.5 (75–90)#	–1 (–7 to 4)	0.513
Postoperative day 3—AM	85 (79.5–93)*	83 (76.5–91)††	3 (–2 to 9)	0.108
Postoperative day 3—PM	82 (76–90)‖‖	84 (76.5–91)§§	–1 (–7 to 5)	0.548

Data reported as number of patients (%) were compared using Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, Fisher exact probability test. Data reported as median (interquartile range) and were compared between groups at the various times using the Mann–Whiney U test. No within-group (*i.e.*, across time) comparisons have been made. n = 62 in the methadone group and n = 53 in the hydromorphone group, except where indicated.

*n = 60. †n = 51. ‡n = 49. §n = 52. ‖n = 61. #n = 50. **n = 59. ††n = 48. ‡‡n = 46. §§n = 40. ‖‖n = 47.

PACU = postanesthesia care unit; Spo_2 = oxygen saturation measured by pulse oximetry.