

Intraoperative Methadone in Surgical Patients

A Review of Clinical Investigations

Glenn S. Murphy, M.D., Joseph W. Szokol, M.D.

The relief of postoperative pain continues to pose a primary therapeutic challenge for clinicians. Despite the development and implementation of novel analgesic strategies over the past several decades, more than 50% of patients experience moderate-to-severe pain, even after “minor” surgical procedures.¹⁻³ Traditionally, shorter-acting opioids like morphine or hydromorphone have been administered as intermittent intravenous boluses to provide postoperative analgesia. However, this approach can produce widely fluctuating blood opioid concentrations, resulting in clinical responses that can range from inadequate pain relief to profound sedation and respiratory depression. Postoperative pain may be more effectively managed with patient-controlled analgesia devices, but this approach requires complex programmed infusion systems, patient cooperation and education, and can also result in significant variability in drug concentrations (a bolus is administered when the patient experiences pain). The use of regional anesthetic techniques can provide high-quality analgesia but is not possible in all patients and may not provide complete pain relief.

Methadone is an alternative opioid with a long half-life that provides stable blood concentrations after a single intraoperative dose, without the fluctuations associated with repeated injections of high clearance agents like morphine or hydromorphone. It is a potent μ -receptor agonist with the longest elimination half-life of the clinically used opioids.⁴ Due to its high oral bioavailability and long duration of clinical effect, methadone is used (along with buprenorphine) for medication-assisted treatment of opioid abuse disorder (oral methadone maintenance replacing intravenous diacetylmorphine [heroin]). The efficacy and safety of methadone has been extensively studied in this setting.⁵ However, there have been relatively few clinical investigations examining the impact of intraoperative methadone use on clinical outcomes.

Methadone is an opioid that possesses several unique properties that may be advantageous in patients undergoing surgical procedures. It has a long elimination half-life of 24 to 36 h.^{6,7} When dosing methadone intraoperatively, the goal is to target blood concentrations in excess of the minimal

analgesic concentration during the slowly declining elimination phase yet below the threshold for respiratory depression (fig. 1).⁴ When smaller doses are administered (5 to 10 mg), methadone acts as a shorter-acting opioid with an analgesic duration of 3 to 4 h (the clinical effect is terminated by redistribution).^{4,6} In contrast, when doses of 20 mg and more are given, the long-elimination half-life closely parallels the clinical effect (approximately 35 h).^{4,6,7} When administered intravenously, methadone has a rapid onset of effect, with central nervous system effect site concentrations rapidly equilibrating with plasma concentrations ($t_{1/2k_{e0}}$ of 4 min).⁸ In addition, methadone is a potent *N*-methyl-D-aspartate (NMDA) receptor antagonist.^{9,10} Activation of the NMDA receptor has been implicated in the development of opioid tolerance, hyperalgesia, and chronic postsurgical pain.^{11,12} Furthermore, methadone inhibits the reuptake of the neurotransmitters serotonin and norepinephrine in the brain^{13,14} and may potentially provide a mood elevation effect in the postoperative period.

The aim of this Clinical Focus Review is to provide an assessment of clinical investigations that have evaluated the effect of intraoperative methadone on postoperative outcomes. Studies included in the review were those that examined intraoperative administration of this long-acting opioid. Clinical trials assessing the efficacy of methadone given *via* other routes of administration (epidural) or used solely as a postoperative analgesic were not included. Unanswered questions relating to the efficacy and safety of methadone in the perioperative setting will be addressed, and evidence supporting optimal dosing regimens for methadone in patients undergoing various surgical procedures will be provided.

Clinical Trials Examining the Effect of Intraoperative Methadone on Postoperative Outcomes

In 1982, Gourlay *et al.*⁶ published a small study describing the effect of a single dose of methadone, administered at induction of anesthesia, on postoperative pain scores and analgesic requirements. Since this initial publication,

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in “This Month in Anesthesiology,” page 1A. For a downloadable PPT slide containing this article’s citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx.

Submitted for publication October 5, 2018. Accepted for publication March 13, 2019. From the Department of Anesthesiology, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, Evanston, Illinois.

Copyright © 2019, the American Society of Anesthesiologists, Inc. All Rights Reserved. Anesthesiology 2019; 131:678–92. DOI: 10.1097/ALN.0000000000002755

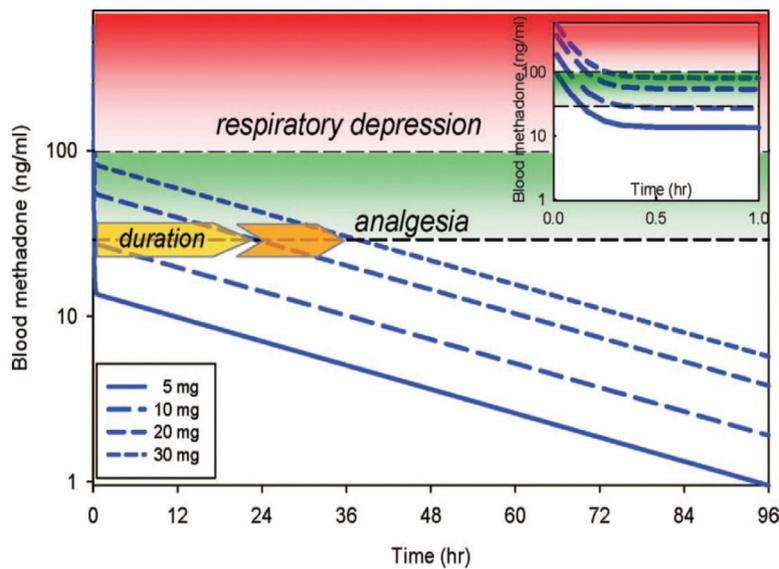


Fig. 1. Relationship between methadone dose and duration of effect. Simulated methadone blood concentrations *versus* time based on pharmacokinetic parameters, the minimal effective analgesic concentration (approximately 30 ng/ml), and the threshold for significant respiratory depression (approximately 100 ng/ml), as determined by Gourlay *et al.*,^{6,7} Data are shown for bolus methadone doses of 5, 10, 20, and 30 mg, with the estimated duration of analgesia of less than 0.5, less than 0.5, approximately 24, and approximately 36 h, respectively. The *inset* shows plasma concentrations for the first hour after dosing. Because of rapid redistribution, anticipated respiratory depression would be less than 30 to 45 min, even at the higher single bolus doses. Reprinted with permission from E. D. Kharasch.⁴

investigations in a variety of patient populations have examined the effect of methadone, administered in the operating room (or operating room and postanesthesia care unit [PACU]), on postoperative recovery. In these clinical trials, analgesic requirements or pain scores were the primary outcome measures (all pain scores were reported on an 11-point verbal analog scale with 0 = no pain and 10 = worst pain imaginable). Despite the use of similar protocols designed to treat postoperative pain in the methadone and control groups, most investigations demonstrated that patients administered methadone had lower pain scores and postoperative narcotic requirements, which was likely due to the prolonged analgesic effects produced by methadone.

Methadone in Patients Undergoing Major Inpatient Surgery

In the first perioperative investigation examining the pharmacokinetics and pharmacodynamics of intraoperative methadone, Gourlay *et al.*⁶ administered 23 subjects (11 spinal fusion patients and 12 general surgical patients) 20 mg of methadone at anesthetic induction. After surgery, 9 subjects (39%) required no postoperative pain medication, 6 subjects (26%) requested nonopioid analgesics (first supplemental dose at 27 h), and 8 subjects required opioid medication (first supplemental dose at 18 h). In a subsequent study, 16 patients (14 undergoing general surgical procedures and 2 undergoing orthopedic surgery) were given 20 mg of methadone

at anesthetic induction, with supplemental methadone provided in the PACU until the patients reported no pain.⁷ In contrast to their earlier study, all of the subjects required additional methadone in the PACU (median dose 10 mg). However, once patients were comfortable, the mean duration of analgesia was 21 h, and mean pain scores were 1.5 on a 0 to 10 scale. The minimum effective blood concentration of methadone was determined to be 57.9 ± 15.2 ng/ml, which was higher than that determined in their earlier investigation (31.6 ± 11.1 ng/ml),⁶ suggesting that the minimal effective concentration may vary in relation to surgical procedure. The same investigators then performed a randomized, double-blinded trial in which 20 patients undergoing upper abdominal procedures were administered either methadone or morphine.¹⁵ Twenty milligrams of either agent were given at anesthetic induction, with 5-mg boluses provided in the PACU and surgical wards until patients were comfortable. Both cohorts required 8 to 9 mg in the PACU to achieve initial pain control. However, the time from initial pain control until the first supplemental dose of opioid needed was significantly longer in the methadone group (21 h) compared to the morphine group (6 h), and total requirements for opioids were lower in the patients given methadone (12 mg *vs.* 41 mg in the morphine group).

In another early clinical trial (1983), 24 patients undergoing elective total hip replacement surgery were randomized to receive 10 mg of methadone at induction of anesthesia

or at the end of the procedure.¹⁶ On postoperative day 1, the requirements for opioid pain medication were approximately two-fold higher in the group given methadone at the end of surgery, suggesting that dosing before the procedure is beneficial.

Two investigations examined the use of methadone in adults undergoing major spine surgery. Gottschalk *et al.*¹⁷ randomized 29 patients to receive either 0.2 mg/kg of methadone at induction or a continuous sufentanil infusion throughout surgery. Forty-eight hours after surgery, opioid requirements and pain scores were approximately 50% lower in the group administered methadone. In a larger investigation enrolling 120 patients, the subjects were randomized to be administered methadone 0.2 mg/kg at the start of surgery or hydromorphone 2 mg at the end of surgery.¹⁸ In the methadone group, opioid requirements were reduced by more than 50%, pain scores were less at 21 of the 27 assessments, and overall satisfaction with pain management was higher, during the first 3 postoperative days when compared to patients given hydromorphone (table 1). Two further methadone studies in pediatric spine patients have been performed (discussed in the Methadone in Pediatric Surgical Patients section).^{19,20}

Intraoperative methadone has also been examined in gynecologic and obstetric patients. In a randomized, double-blinded investigation in hysterectomy patients, Chui and Gin²¹ administered either 0.25 mg/kg of methadone or morphine at anesthetic induction, with further increments given in the PACU if analgesia was required. The mean total doses of methadone (0.43 mg/kg) and morphine (0.45 mg/kg) required did not differ between groups. However, 10 of the 15 patients given methadone required no further postoperative morphine, and pain scores on a 0 to 10 scale were lower for the first 48 h in this group (1 to 2 *vs.* 3 to 5 in the morphine group). In another single-blinded investigation in

women undergoing hysterectomies, 40 patients were randomized to receive either 20 mg of morphine or methadone at induction of anesthesia, with the same drug given for pain in the PACU and surgical wards for analgesia.²² Patients in the methadone cohort required less opioid in the PACU (2.0 mg *vs.* 4.4 mg) and on the wards (4.5 mg *vs.* 42.3 mg), and pain scores on a 0 to 10 scale were less in this group (1.9 *vs.* 3.4), compared to the morphine cohort, over the 72-h study period. A further retrospective case-control investigation examining outcomes in elective or emergent caesarian deliveries compared 25 patients administered methadone (mean dose of 0.17 mg/kg) to 50 control subjects receiving fentanyl, morphine, or both.²³ Patients in the methadone cohort reported lower pain scores and required 40% less opioids in the first 48 postoperative h.

The analgesic effects of methadone have also been examined in cardiac surgical patients. Two studies from Brazil compared recovery from cardiac surgery in patients randomized to receive either methadone or morphine. In a double-blinded investigation, Udelsmann *et al.*²⁴ administered patients 20 mg of methadone, 20 mg of morphine, or saline (control) after induction. Compared to the other two groups, patients administered methadone required significantly less postoperative analgesics (45% needed none), and pain scores on a 0 to 10 scale were less (0.5 *vs.* 2.8 in the control group) in the first 24 postoperative h. Carvalho *et al.*²⁵ randomized 100 patients to be given 0.1 mg/kg of methadone or morphine at the end of cardiac surgery. Significantly fewer patients required postoperative opioids in the methadone group (29% *vs.* 43% in the morphine cohort), and pain scores on a 0 to 10 scale were reduced in this group at 24 h (1.9 *vs.* 2.9 morphine cohort).

In the largest intraoperative clinical trial using methadone, Murphy *et al.*²⁶ randomized 156 cardiac surgical

Table 1. Postoperative Analgesic Requirements in the Investigation by Murphy *et al.*¹⁸

	Hydromorphone, mg		Difference (99% CI)	P Value
	Methadone Group	Hydromorphone Group		
PACU	1 (0.5 to 1.6)	1.85 (1 to 2.35)*	-0.6 (-1.1 to -0.1)	0.001
First 24 h	4.56 (2.3 to 7.1)	9.9 (6.45 to 13.2)	-4.8 (-6.9 to -2.6)	< 0.0001
Second 24 h	0.60 (0 to 2.8)†	3.15 (0.75 to 8.2)*	-2 (-3.9 to -0.2)	< 0.001
Third 24 h	0 (0 to 0.05)‡	0.35 (0 to 3.4)§	-0.125 (-0.6 to 0)	< 0.001
Total	5.85 (3.1 to 9.8)	14.6 (9.8 to 23.3)	-8.2 (-12.1 to -4.5)	< 0.0001
Oral pain tablets				
First 24 h	1 (0 to 2)	2 (1 to 3)	-1 (-1 to 0)	0.057
Second 24 h	3 (1 to 4)†	4 (2 to 7)*	-2 (-3 to 0)	0.005
Third 24 h	3 (1 to 5)‡	6 (3 to 9)§	-3 (-5 to -1)	0.0001
Total	7.5 (4 to 12)	12 (6 to 18)	-4 (-8 to -1)	0.001

The data are reported as medians (interquartile range) and were compared between groups at the various times using the Mann-Whitney U test. No within-group (*i.e.*, across time) comparisons have been made. The oral pain tablets contained 10 mg of hydrocodone with 325 mg of acetaminophen. n = 62 in the methadone group, and n = 53 in the hydromorphone group, except where indicated. Reprinted with permission from Murphy *et al.*¹⁸

*n = 52. †n = 61. ‡n = 60. §n = 48.

PACU, postanesthesia care unit.

patients to be given either 0.3 mg/kg methadone or 12 μ g/kg fentanyl before cardiopulmonary bypass. Postoperative opioid requirements and pain scores were reduced by approximately 40% during the first 3 postoperative days in the methadone group, and patient satisfaction with pain management on a 100-mm verbal analog scale was higher in these subjects (90 to 100 vs. 70 to 90 in the fentanyl group). These findings demonstrated that despite a long time period between anesthetic induction and tracheal extubation in the intensive care unit, a dose of methadone given before surgery provided a prolonged analgesia benefit (Porter *et al.*¹⁶ observed that patients administered methadone at induction of anesthesia had postoperative opioid requirements that were approximately 50% less than those given methadone at the end of surgery).

Lower-dose Methadone in Ambulatory Surgical Patients

A smaller dose of methadone may be effective in producing long-lasting analgesia in patients undergoing ambulatory surgical procedures. Simoni *et al.*²⁷ randomized 126 patients undergoing laparoscopic surgery to receive either 0.1 mg/kg methadone, 2 μ g/kg clonidine, or normal saline (control) before the procedure. A total intravenous anesthetic technique with remifentanyl (which may promote acute tolerance and hyperalgesia)²⁸ was used in all subjects. The number of patients with pain in the immediate postoperative period was significantly lower in the methadone group compared to the clonidine and control groups (approximately 50% less).

The efficacy and safety of methadone in ambulatory surgical patients (most undergoing laparoscopic cholecystectomy, tubal ligation, salpingectomy, oophorectomy, or salpingectomy with oophorectomy) was assessed in a randomized, double-blinded, dose-finding study.²⁹ At induction of anesthesia, 40 patients were administered methadone (initially 0.1 mg/kg ideal body weight and then 0.15 mg/kg ideal body weight), and 20 patients were given standard shorter-acting opioids (controls). Opioid consumption, pain intensity, and opioid side effects were assessed in the hospital and for 30 days postoperatively using home diaries. In-hospital nonmethadone opioid use (morphine equivalents) was less in patients given 0.1 and 0.15 mg/kg of methadone (7.1 and 3.3 mg, respectively) compared to the control group (35.3 mg, $P < 0.001$). In the first 30 postoperative days, patients administered 0.15 mg/kg methadone reported less pain at rest ($P = 0.02$) and used fewer opioid pills than controls (5 vs. 10, $P < 0.0001$).

Methadone in Pediatric Surgical Patients

The pharmacokinetics of methadone in adolescents undergoing major spine surgery was examined in two investigations. In the first, 31 children (ages 5 to 18 yr) received a dose of 0.1, 0.2, or 0.3 mg/kg of methadone at anesthetic induction.¹⁹ This cohort was compared to a similar group

not administered methadone. Methadone pharmacokinetics were linear over the dose range studied (fig. 2). Although analgesic requirements were reduced with increasing doses of methadone, the differences were not statistically significant; however, the study was likely underpowered to detect differences in this secondary endpoint. A similar study was performed in 17 adolescents (ages 12 to 19 yr) given 0.25 mg/kg of methadone before surgical incision.²⁰ The authors observed that the mean methadone concentration was less than 58 μ g/L⁻¹ by the first hour after administration (a previous investigation established the minimum effective blood concentration for analgesia was 58 μ g/l for more painful operations);⁷ the authors recommended that additional methadone should be administered to ensure adequate plasma concentrations for 24 h. Pain scores and analgesic requirements were not reported in this investigation.

A double-blinded study in 35 children (ages, 3–7 yr) undergoing major surgical procedures randomized subjects to either 0.2 mg/kg of methadone or morphine at induction, with supplemental doses of the same agent provided for analgesia in the PACU.³⁰ During the first 3 postoperative days, fewer patients in the methadone group had severe pain scores (18%) compared to the morphine group (35%), and analgesic requirements were less in the methadone cohort. An addition retrospective investigation examined four types of anesthesia for pediatric patients undergoing the Nuss procedure for correction of pectus excavatum: general anesthesia with standard short-acting opioids, epidural with general anesthesia, multimodal anesthesia (ketamine, dexmedetomidine, and clonidine patch), and multimodal

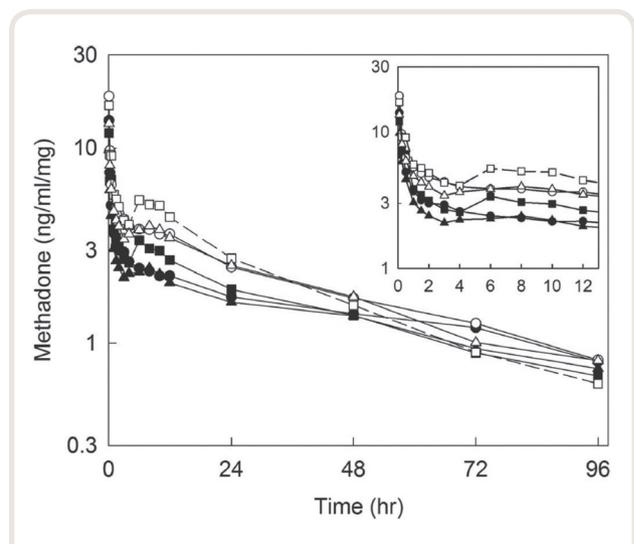


Fig. 2. Dose-adjusted plasma concentrations of methadone after intravenous administration.¹⁹ Subjects received 0.1 (circles), 0.2 (squares), or 0.3 (triangles) mg/kg of racemic (*R,S*)-methadone hydrochloride. Solid symbols and lines show *R*-methadone, and open symbols and dotted lines show *S*-methadone. Each data point is the mean. The inset shows the period from 0 to 12 h. Reprinted with permission from Sharma *et al.*¹⁹

anesthesia with methadone (0.1 mg/kg).³¹ Compared to the other three groups, patients in the multimodal anesthesia cohort with methadone had the lowest total postoperative opioid use (50% less than the epidural group), the least time with uncontrolled pain, and the shortest hospital length of stay.

Important Limitations of Published Clinical Trials

Studies examining the use of methadone in the perioperative setting have documented that a single dose administered intraoperatively produces a prolonged analgesic effect that can persist during the period of the most intense postoperative pain (postoperative days 1 through 3). Despite this encouraging research, there are limitations to many of the clinical trials. Most importantly, the majority of prospective clinical studies enrolled only a small number of patients. Only 4 investigations enrolled 100 patients or more, and 11 of the remaining 13 investigations examined less than 50 subjects. Such small sample sizes can produce false positive results or overestimate the magnitude of an association. Furthermore, only a few investigations examined the potential analgesic benefits of methadone in conjunction with other opioid-sparing agents. At the present time, there is a need for larger-scale, double-blinded investigations to define the efficacy and safety of intraoperative methadone. The limitations of the published research are presented in table 2.

Safety of Intraoperative Methadone

A primary concern related to the use of long-acting opioids is the potential for prolonged respiratory depression. In randomized trials, no differences in the incidence of respiratory depression (respiratory rates less than 8 to 12 breaths/min) or hypoxemic events (oxygen saturations less than 92 to 90%) were observed between methadone and control groups during the PACU admission, on the surgical wards, or in the intensive care unit.^{15,18,19,21,22,24–26,29,30} Similarly, no episodes of adverse respiratory events were reported in patients administered intraoperative methadone in observational or retrospective investigations.^{6,7,16,20,23,31} No patients given methadone required naloxone infusions for prolonged respiratory depression.

Clinical trials suggest that methadone does not appear to increase the risk of other opioid-related side effects. Studies that have assessed patients for level of postoperative sedation have documented that no differences existed between subjects administered intraoperative methadone and those given conventional opioids.^{18,19,21,22,26,29,30} The observed incidences of postoperative nausea and vomiting did not differ between the methadone and control groups, with the exception of a higher risk in methadone patients in the PACU (but not on the wards) noted by Chui *et al.*²¹ and a lower risk in methadone patients in the intensive care unit observed by Udelsmann *et al.*²⁴ No adverse cardiac

events related intraoperative methadone administration have been described in the published literature. Only one investigation examined the effect of methadone on bowel function (no differences were observed between the methadone and hydromorphone groups in the time to first flatus or bowel movement after spine surgery).¹⁸ However, it is important to note that the majority of these clinical trials were small and not powered to assess safety outcome measures, particularly rare events such as significant respiratory depression. In addition, high-risk patients were excluded from enrollment in many studies. Although limited data from randomized studies suggest that the risks of methadone do not exceed conventional shorter-acting opioids, additional information from larger-scale investigations is needed (particularly related to respiratory depression).

One case report from 1976 describes an 81-yr-old female with normal renal and hepatic function who received 30 mg of methadone (0.7 mg/kg) for a mitral valve procedure.³² The patient was extubated after receiving 1.0 mg of naloxone and subsequently required additional naloxone every 2 to 4 h for the next 8 days. The prolonged effect was likely related to the large dose given and the patient's advanced age.

Dunn *et al.*³³ published a retrospective review of perioperative adverse events in patients administered intraoperative methadone (mean dose, 11.5 mg) for major spine surgical procedures. The records of 1,478 patients undergoing these operations over a 5-yr period were examined. Respiratory depression (fewer than 8 breaths/min) was observed in 37% of patients, and hypoxemia (oxygen saturation less than 90% or the need for more than 2 l of nasal cannula oxygen flow to maintain oxygen saturation at greater than 96%) was noted in 80% of patients. Naloxone was needed in 2% of patients, and 1.5% required reintubation. Although a high incidence of adverse events was described in this investigation, an important limitation is that the study did not include a propensity-matched control group given shorter-acting opioids.

Several synthetic opioids, such as methadone, inhibit the serotonin transporter at clinically relevant concentration, resulting in increases in intrasynaptic levels of serotonin.³⁴ Case reports have described the development of serotonin syndrome in patients on chronic methadone maintenance therapy administered other serotonergic medications including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants.³⁴ Serotonin syndrome has not been reported in patients administered intravenous methadone perioperatively. However, serotonin syndrome should be suspected if a patient on antidepressants given methadone develops altered mental status, autonomic instability (fever, tachycardia), or neuromuscular abnormalities (rigidity, tremor, clonus) in the perioperative period.

Table 2. Methadone Investigations 1982–2018: Study Designs, Findings, and Limitations of the Clinical Trials

Study, Year	Trial Design	Enroll, n	Type of Surgery	Dose of Methadone	Total Methadone	Total Intraoperative Opioid Used			Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
						Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used Postoperatively					
Gourlay <i>et al.</i> ⁶ 1982	Observation	23	General/orthopedic surgical procedures	20 mg at induction of anesthesia	20 mg	No control group	No control group	Variety of narcotics, 39% of patients required no postoperative analgesics, 26% required only nonnarcotic analgesics	Not reported	Median duration of analgesia was 27 h from 20 mg of methadone	No differences between groups	Small sample size, not randomized, no control group, exclusion criteria not listed, primary and secondary outcomes not defined, no calculation of sample size, postoperative analgesic treatment not standardized, limitations not described	
Gourlay <i>et al.</i> ⁷ 1984	Observation	16	General/orthopedic surgical procedure	20 mg at anesthetic induction; 5-mg supplemental doses in the PACU or wards	42 ± 10 mg	No control group	No control group	Only five patients required additional analgesics within the first 20 postoperative h	Mean 1.5 ± 1.3	Median duration of analgesia was 21 ± 13 h	No differences between groups	Small sample size, not randomized, no control group, exclusion criteria not listed, primary and secondary outcomes not defined, no calculation of sample size, limitations not described	
Gourlay <i>et al.</i> ¹⁵ 1986	Randomized, double-blinded	20	General surgical (abdominal)	20 mg at anesthetic induction; 5-mg additional doses in the PACU or wards	40 ± 11 mg	20 mg of morphine at anesthetic induction, 5-mg supplemental doses in the PACU and wards	70 ± 21 of morphine	Doses of methadone or morphine on the surgical wards were 11.5 ± 8.5 in methadone group; 41 ± 14.1 in morphine group	No differences between groups	Time until first requirement for analgesia on the wards was 21 h in the methadone group and 6 h in the morphine group	No differences between groups	Small sample size, type of general surgical procedure not standardized, method of randomization not clarified, exclusion criteria not listed, primary and secondary outcomes not defined, no calculation of sample size, limitations not described	
Porter <i>et al.</i> ¹⁶ 1983	Randomized, unblinded	24	Hip replacement surgery	Patients randomized to receive either 10 mg methadone at induction or the end of surgery	10 mg	No control group	No control group	Demand rate for methadone was two times higher in the group given methadone at the end of surgery	Not reported	No differences in respiratory outcomes between groups	No differences between groups	Small sample size, unblinded, method of randomization not clarified, no control group, postoperative pain scores not assessed, primary and secondary outcomes not defined, no calculation of sample size, limitations not described	

(Continued)

Downloaded from http://ajph.spubs.aaph.org/doi/pdf/10.1131/67/8/525657/20190900_0-00037.pdf by guest on 05 February 2024

Table 2. (Continued)

Study, Year	Trial Design	Enroll, n	Type of Surgery	Dose of Methadone	Total Methadone	Total			Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
						Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used Postoperatively					
Gottschal <i>et al.</i> ¹⁷ 2011	Randomized, single-blinded	29	Complex spine surgery	0.2 mg/kg before surgical incision	15 ± 3.3 mg	Sufentanil bolus of 0.75 µg/kg; infusion of 0.75 µg · kg ⁻¹ · h ⁻¹ during the procedure	175 ± 56 µg of sufentanil	PCA fentanyl, morphine, hydromorphone - converted morphine equivalents	Morphine equivalents approximately 50% less at 48 and 72 h in the methadone compared to the sufentanil group	Pain scores approximately 50% less at 48 h in the methadone group compared to sufentanil group	Greater differences between groups in postoperative analgesia were observed at 48 and 72 h, compared to 24 h	No differences between groups	Small sample size, anesthetologists were not blinded to group assignment, primary and secondary outcomes not clearly defined, postoperative analgesic management not standardized
Murphy 2017	Randomized, double-blinded	120	Complex spine surgery	0.2 mg/kg actual body weight at induction of anesthesia	17 ± 4 mg	2 mg of hydromorphone	2 mg of hydromorphone	PCA hydromorphone	Hydromorphone requirements were reduced by 60% in subjects randomized to receive methadone compared to hydromorphone	Pain scores reduced by 30%–40% on PODs 1–3 in the methadone group compared to hydromorphone group	Overall satisfaction with pain management was significantly higher in methadone group	No differences between groups	Two opioids administered at different times during the procedure
Chui and Gin ²¹ 1992	Randomized, double-blinded	30	Abdominal hysterectomy	0.25 mg/kg at induction of anesthesia; 3 to 4.5 mg boluses in the PACU	25 mg	0.25 mg/kg of morphine at anesthetic induction; 3–4.5 mg boluses in the PACU	25 mg of morphine	Morphine	67% of patients given methadone required no further pain medication on PODs 1 and 2; 100% of patients given morphine required at least two doses of postoperative pain medication	Patients in the methadone group had lower pain scores on PODs 1 and 2 compared to the morphine group	Patients in the morphine group had a higher increase in heart rate after tracheal intubation	Higher incidence of emetic symptoms in the methadone group in the PACU but not on the wards	Small sample size, method of randomization not clarified, primary and secondary outcomes not defined, no calculation of sample size, limitations not described
Richlin and Reubent ²² 1990	Randomized, single-blinded	40	Abdominal hysterectomy	20 mg at induction; subsequent dosing in the PACU and surgical wards (same agent)	27 ± 6 mg	20 mg of morphine at induction; subsequent dosing in the PACU and surgical wards (same agent)	67 ± 15 mg of morphine	Same drug as used in the operating room (methadone or morphine)	Analggesic requirements reduced by 60% in the methadone group compared to the morphine group	1.9 ± 0.3 methadone group; 3.4 ± 0.5 morphine group during POD 1–3	In the methadone group, 65% required no analgesics in the PACU, and 35% required no further opioids for POD 1–3	No differences between groups	Small sample size, single-blinded, method of randomization not clarified, exclusion criteria not listed, primary and secondary outcomes not defined, no calculation of sample size, limitations not described

(Continued)

Table 2. (Continued)

Study, Year	Trial Design	Enroll, n	Type of Surgery	Dose of Methadone	Total Methadone	Total Intraoperative Opioid Used in the Control Group		Intraoperative Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
						Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used in the Control Group						
Russell et al. ²³ 2013	Retrospective	75	Cesarean sections under general anesthesia	7 to 20 mg	14 ± 5 mg (0.17 mg/kg)	Intravenous fentanyl, morphine, or both	15 ± 11 mg of morphine equivalents	PCA fentanyl or morphine—converted to morphine equivalents	Total postoperative opioid consumption in morphine equivalents: 115 ± 94 mg in the methadone group; 213 ± 104 in control group	Pain scores less in PACU but not on POD 1–2 in the methadone group, compared to control group	No differences between groups in PACU or hospital length of stay	No differences between groups	Retrospective study design, clinicians and investigators not blinded to group assignments, no calculation of sample size, dosing of methadone and fentanyl/morphine in the control group not standardized, postoperative analgesic management not standardized
Udelsmann et al. ²⁴ 2011	Randomized, double-blinded	55	Cardiac surgery	20 mg at anesthetic induction	20 mg	Either 20 mg of morphine or saline (control)	20 mg of morphine or 2 ml of saline	0.03 mg/kg of morphine	45% of the methadone patients, 26% of the morphine patients, and 11% of the control patients required no postoperative morphine in first 24 h	Pain scores less in the methadone group compared to the other two groups	The number of redoses required was significantly higher in the control group compared to the other two groups	Incidence of emetic symptoms less in the methadone group	Small sample size, details of sample size analysis not provided, details of randomization assignments not provided, patients followed for only 24 h after surgery
Carvalho et al. ²⁵ 2018	Randomized, double-blinded	100	Cardiac surgery	0.1 mg/kg, adjusted body weight, at end of surgery	Not stated	0.1 mg/kg of morphine, adjusted body weight, at the end of surgery	Not stated	0.03 mg/kg of morphine	In the first 36 h, 43% of the patients in the morphine group required analgesics, compared to 29% in the methadone group	Pain scores lower at 24 h in the methadone group compared to the morphine group	Time to first request for analgesics was longer in the methadone group	No differences between groups	Exclusion criteria not defined, patients only followed for 36 postoperative h, pain scores assessed only at 12, 24, and 36 h
Murphy et al. ²⁶ 2015	Randomized, double-blinded	156	Cardiac surgery	0.3 mg/kg before cardiopulmonary bypass	Not stated	12 µg/kg of fentanyl prior to cardiopulmonary bypass	Not stated	Morphine	Total dose of postoperative morphine lower in the methadone vs. fentanyl group over PODs 1–3	Pain scores reduced by 30%–40% in the methadone vs. fentanyl group	Time to first morphine rescue longer in the methadone group; overall satisfaction with pain management significantly higher in the methadone group	No differences between groups	Doses of fentanyl and methadone may have not been equivalent

(Continued)

Table 2. (Continued)

Study, Year	Trial Design	Enroll, n	Type of Surgery	Dose of Methadone	Total Methadone	Total Intraoperative Opioid Used in the Control Group		Intravenous Opioid Used Postoperatively	Postoperative Analgesic Requirements	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
						Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used in the Control Group						
Sharma <i>et al.</i> ¹⁹ 2011	Dose-escalation protocol	62	Complex spine surgery—adolescents	0.1, 0.2, or 0.3 mg/kg	6.1 ± 1.3 mg, 9.9 ± 1.4 mg, 17.4 ± 2.3 mg, in the three groups, respectively	81 ± 39 of morphine equivalents	Variety of PCA opioids	No significant differences between groups	No significant differences between groups	No differences between groups	Pharmacokinetics were linear over the dose range studied (0.1–0.3 mg/kg)	No differences between groups	Small sample size, unblinded (primarily a pharmacokinetic investigation), not randomized, not powered to examine pain scores and analgesic requirements, doses of methadone may have been insufficient to control pain after complex spine surgery
Stemland <i>et al.</i> ²⁰ 2013	Observation pharmacokinetic study	20	Complex spine surgery—adolescents	0.25 mg/kg at induction of anesthesia	Not stated	No control group	Not stated	Not assessed in the investigation	Not assessed in the investigation	Rapid redistribution after a bolus administration may have resulted in plasma concentrations that were inadequate in providing postoperative analgesia	Not assessed	Small sample size, not randomized, no control group, pain scores and analgesic requirements not assessed, postoperative complications not reported, limitations of investigation not described	
Berde <i>et al.</i> ²⁰ 1991	Randomized, double-blinded	35	Major surgical procedures—children	0.2 mg/kg at induction; 0.05 mg/kg in the PACU for pain	Not stated	Not stated	0.1 mg/kg of morphine as needed	Opioid requirements on the operative day reduced by 47% in the methadone vs. morphine group	Postoperative pain less in the methadone vs. morphine group over the 36-h observation	No differences between groups	No patients had delayed emergence from anesthesia	No differences between groups	Small sample size, types of surgical procedures not standardized, power analysis not performed for sample size calculation, primary outcome measure not clearly defined, limitations of study not reported
Singhal <i>et al.</i> ²¹ 2016	Retrospective	125	Nuss procedure—children	0.1 mg/kg at induction + multimodal pain management	Not stated	General, general anesthesia + epidural, multimodal anesthesia	PCA morphine	Total opioid requirements less in multimodal anesthesia + methadone group compared to other three groups	Severe pain scores less in multimodal anesthesia + methadone group compared to other three groups	No differences between groups	Hospital length of stay was less in the multimodal anesthesia + methadone group compared to the other three groups	No differences between groups	Retrospective study design, primary outcome variable not clearly defined, clinicians and investigators not blinded to group assignments, no calculation of sample size, change in surgical technique over time

(Continued)

Table 2. (Continued)

Study, Year	Trial Design	Enroll, n	Type of Surgery	Dose of Methadone	Total Methadone	Total Intraoperative Opioid Used		Intravenous Opioid Used Postoperatively	Postoperative VAS Pain Scores on an 11-Point Scale	Other Findings	Postoperative Complications	Limitations of the Study Design
						Intraoperative Opioid Used in the Control Group	Intraoperative Opioid Used in the Study Group					
Simoni <i>et al.</i> ²⁷ 2009	Randomized, double-blinded	126	Video laparoscopic procedures	0.1 mg/kg at induction	Not stated	2.0 µg/kg of clonidine (control) or saline (control)	Not stated	Intravenous tramadol	The incidence of pain over the 2 h in PACU was significantly less in the methadone group compared to the other two groups	Clonidine before surgery did not reduce the incidence of postoperative pain	No differences between groups	Primary endpoint not clearly defined, pain scores only evaluated in the PACU, analgesic requirements not reported
Komen ²⁸ 2019	Randomized, double-blinded, dose-escalation protocol	60	Laparoscopic ambulatory surgical procedures	0.1 or 0.15 mg/kg ideal body weight at anesthetic induction	5.5 or 8.5 mg, respectively	Variety of short-acting opioids	25 mg of morphine equivalents	Fentanyl or hydromorphone	No differences between groups	For the first 30 days after surgery, pain scores at rest and need for oral opioid medications were less in the 0.15 mg/kg methadone group	No differences between groups	Small sample size, type of opioid not standardized in the control group
Dunn ³³ 2018	Retrospective	1,478	Complex spine surgery	2 to 40 mg	11.7 ± 4.7 mg	No control group	No control group	PCA hydromorphone	Not reported	Naixone was administered to 2.3% of patients	37% had respiratory depression 80% had hypoxemic events	Retrospective study design, no control group, perioperative management not standardized, dosing of methadone not standardized, exclusion criteria not listed, primary and secondary outcomes not defined, no calculation of sample size

PACU, postanesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; VAS, verbal analog scale on an 11-point scale where 0 = no pain and 10 = worst pain imaginable.

Pharmacogenomics of Methadone Metabolism

There may be considerable interindividual and intraindividual variability in the disposition of methadone, which may be related to genetic polymorphism of hepatic cytochrome P450 genes. Methadone is cleared primarily by P450 (CYP)-catalyzed *N*-demethylation to inactive 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine and a small amount of urinary excretion of the unchanged drug.³⁵ The P4502B6 (CYP2B6) genotype affects plasma metabolism and clearance, with certain allele carriers (CYP2B6*6) having higher methadone concentrations and slower elimination, whereas other carriers (CYP2B6*4) have faster elimination and lower plasma concentrations.³⁵ However, this effect is significantly greater after oral methadone administration compared to intravenous administration (which may explain the unpredictability of methadone dosing when initiating oral therapy). In addition, medications that may induce (phenobarbital, phenytoin) or inhibit (fluoxetine, sertraline, ticlopidine) CYP2B6 may potentially influence plasma concentrations of methadone.

Questions to Be Addressed in Future Research

What Is the Optimal Dose of Methadone to Be Administered to Patients Undergoing Various Surgical Procedures?

The dose of methadone that will result in prolonged analgesia without inducing respiratory depression has not been clearly defined in the literature. Furthermore, the minimal effective concentration of methadone required for pain relief may vary dependent upon the surgical procedure.^{6,7} In the initial investigation by Gourlay *et al.*,⁶ 20 mg was administered at induction, with subsequent studies by this group administering an additional dose of 8 to 10 mg in the PACU to achieve sustained analgesia.^{7,15} A variety of doses have been used in clinical trials, ranging from 0.1 to 0.3 mg/kg, with the majority of studies using a dose of either 0.2 mg/kg or a fixed dose of 20 mg.

With the exception of the investigation by Sharma *et al.*,¹⁹ dose–response studies of methadone in the perioperative period have not been performed. It is likely that more painful operations (major spine surgery) require larger doses of methadone, and the administration of 0.25 to 0.3 mg/kg may be insufficient.^{19,20} In the pharmacokinetic study by Stemland *et al.*,²⁰ few patients maintained steady-state plasma levels above those recommended in Gourlay *et al.*, for painful procedures (58 ng/ml). Simulation modeling in this investigation suggested that a significantly higher dose of intraoperative methadone (a second bolus of 0.35 mg/kg of methadone at 4 h) would be required to achieve sustained plasma concentrations for 24 h (or alternatively providing subsequent dosing based upon pain severity [0.03 mg/kg for mild pain and 0.05 mg/kg for severe pain every 4 h]). In contrast, other studies have documented a significant opioid-sparing effect from doses as low as 0.1 mg/kg

of methadone in patients undergoing major surgical procedures^{25,31} (although the analgesic benefit of this lower dose was relatively modest in the investigation by Carvalho *et al.*,²⁵ and the study by Singhal *et al.*³¹ used methadone 0.1 mg/kg as a component of a multimodal pain management strategy). In laparoscopic surgical patients, doses of 0.1 to 0.15 mg/kg ideal body weight may provide sufficient analgesia with no side effects (median dose of 9 mg in the higher-dose group).²⁹

Only three studies reported whether methadone was dosed on actual or ideal body weight.^{18,25,29} Interpatient variability in dosing may be minimized if ideal body weight is used, yet may result in minimal effective blood concentrations below the threshold for analgesia in some patients. In contrast, dosing on actual body weight in obese patients may result in high blood concentrations of methadone that result in prolonged respiratory depression. The administration of methadone may be simplified by giving a standard dose at induction (10 or 20 mg), dependent upon the expected degree of postoperative pain.

Determining appropriate dosing of methadone may be further complicated in the opioid-tolerant patient. Patients presenting for certain surgical procedures (complex spine surgery) are often prescribed potent opioids for preexisting neuropathic pain. These patients will likely benefit from larger doses of intraoperative methadone; however, appropriate dosing is dependent upon the degree of tolerance that is present at the time of surgery. Titration of additional methadone in the PACU, based upon degree of sedation and respiratory rate, may be of particular benefit in this patient population.^{7,15}

Is Methadone Safe in High-risk Patient Populations?

With the exception of studies performed in cardiac surgical patients, clinical trials examining perioperative methadone use have enrolled relatively healthy patients without significant medical comorbidities. The safety of methadone in a higher-risk patient population (the elderly, those who are morbidly obese, or those with cardiovascular disease) has not been documented in the published literature. Gouley *et al.*⁶ observed that the methadone terminal half-life was positively correlated with patient age, which suggest that more careful dosing of methadone is required in the elderly.

The efficacy and safety of methadone has not been specifically assessed in morbidly obese patients, although these patients were not excluded from many clinical trials. Obese patients, particularly those with obstructive sleep apnea, may have a greater sensitivity to the respiratory depressant effects of opioids, although high-quality evidence supporting this belief is lacking.³⁶ More cautious dosing and monitoring of the effects of methadone may be required in this patient population. It is possible, however, that by reducing the number of supplemental doses of opioids used postoperatively, intraoperative methadone may attenuate the risk of hypoventilation and hypoxemia after surgery. Further

studies are required to define optimal dosing practices in this patient population.

Is Intraoperative Methadone Associated with an Increased Risk of QT Prolongation and Cardiac Arrhythmias?

Patients receiving methadone maintenance therapy for opioid dependence disorder have an increased risk of QT prolongation, torsade de pointes, and cardiac death.³⁷ The potential for QT prolongation and the development of arrhythmias appears to be directly related to dose and chronicity of use in this patient population.³⁷ The effect of a single intravenous dose of methadone on the QT interval and risk of arrhythmias has not been specifically defined in a randomized trial. However, a higher incidence of adverse cardiac events has not been observed in patients administered perioperative methadone in clinical studies, and a systematic review of case reports of torsade de pointes did not describe this event after intraoperative methadone use.³⁸ However, conclusions relating to cardiac safety are limited by the small size of the majority of clinical trials.

In an independent ancillary study to the VINO trial, Nagele *et al.*³⁹ examined surgical and anesthetic factors (drugs, stress, hypothermia, electrolyte disturbances) associated with QTc (QT interval corrected for heart rate) prolongation in 469 patients undergoing major noncardiac surgery. In the PACU, a QTc interval of 440 ms or more was observed in 51% of patients, which resolved in all subjects by the first postoperative day. A number of medications used in the perioperative period were associated with QTc prolongation, including methadone (mean change in QTc interval of 30.7 ms). In a retrospective analysis of 1,478 patients given methadone (in addition to other perioperative medications affecting the QT interval) for major spine surgery, 58.8% of patients demonstrated QTc prolongation on a postoperative electrocardiogram (defined as more than 440 ms for men or more than 460 ms for women).³³ Torsade de pointes was not observed in any patients.

Does Methadone Use in the Operating Room Reduce the Risk of Development of Chronic Postsurgical Pain?

Acute pain after surgery is a primary risk factor for the development of chronic postsurgical pain, which is observed in 10 to 50% of patients.⁴⁰ Furthermore, pain triggers NMDA receptor activation, resulting in prolonged increases in nociceptive transmission. This process has been postulated to contribute to hyperalgesia and allodynia and the transition from acute to chronic pain.⁴¹ There are some studies that suggest that use of intraoperative ketamine, a potent NMDA antagonist, can reduce the development of chronic postsurgical pain 3 and 6 months after surgery.⁴² At the present time, however, there is only limited evidence documenting that any perioperative agent can consistently reduce the risk of chronic pain after surgery.

Methadone is a NMDA antagonist like ketamine^{9,10} and has also been documented to reduce the intensity of postoperative pain. Therefore, it is possible that a single dose of intraoperative methadone may have a preventive analgesic effect and decrease the risk of the development of chronic postsurgical pain. Komen *et al.*²⁹ observed that ambulatory patients given 0.15 mg/kg of methadone at anesthetic induction had significantly less pain at rest and required fewer oral opioids for the first 30 days after surgery compared to those given shorter-acting intraoperative opioids. Longer-term follow-up for the development of chronic postsurgical pain was not conducted in this study or in most other investigations examining perioperative methadone use (1-yr follow-up is currently being conducted in two investigations in cardiac and spine patients).^{18,26}

What Is the Risk of Postoperative Respiratory Depression Associated with Methadone, When Compared with Shorter-acting Opioids?

Clinicians may have concerns that the long half-life of methadone may contribute to prolonged sedation and respiratory depression. Clinical trials have not supported this belief. However, continuous pulse oximetry and respiratory rate monitoring was not used in any of the investigations for the first 24 to 72 postoperative h to compare the incidences of adverse respiratory events between methadone and control groups, and studies were not adequately powered to assess this important outcome measure. A retrospective analysis of a large cohort of patients undergoing major spine surgery reported that 37% of patients given methadone experienced postoperative respiratory depression.³³ However, this cohort was not compared to a control group not administered methadone. Furthermore, all patients were given additional opioids intraoperatively and likely required a significant amount of intravenous hydromorphone after major, multilevel spine surgery (data not reported).

If naloxone is required in the PACU for methadone-induced respiratory depression, an infusion should be considered. The half-life of naloxone (approximately 90 min) is considerably shorter than that of methadone (35 h with a dose of 20 mg). Recurrent respiratory depression has been reported in a patient given a single dose of naloxone after cardiac surgery.³²

Is There a Role for Methadone in Enhanced Recovery after Surgery Protocols?

An important component of most enhanced recovery after surgery protocols is a reduction in the use of intra- and postoperative opioids, primarily to minimize the adverse effects of these medications on respiratory and bowel function. Only one study has specifically addressed the effect of methadone on postoperative bowel function.¹⁸ The reduction in need for postoperative opioids associated with methadone use may provide a beneficial effect on bowel

motility. In contrast, the prolonged elimination phase of methadone may adversely affect recovery of bowel motility. Further research is needed to determine the effect of methadone on bowel function, patient-perceived quality of recovery, hospital length of stay, and outcomes after discharge in enhanced recovery after surgery protocols. At the present time, only one published investigation has examined the use of methadone as part of an enhanced recovery after surgery pathway (in patients undergoing spinal fusion for idiopathic scoliosis).⁴³

Many of the clinical trials examined the effect of methadone on postoperative analgesia in the absence of other opioid-sparing agents to avoid the potential confounding effects of these other agents. In the investigation by Singhal *et al.*,³¹ the addition of methadone to a standardized multimodal approach to pain management resulted in lower pain scores, decreased analgesic requirements, and a shorter hospital length of stay. Furthermore, studies that included the addition of other opioid-sparing agents in both the methadone and control treatment groups reported that pain scores and analgesic use were less in the methadone groups.^{18,23} Additional investigations are needed to define the role of methadone as part of a multimodal treatment strategy for postoperative pain and enhanced recovery.

Caution may be required when methadone is combined with other agents as part of an enhanced recovery after surgery protocol. The administration of opioids with gabapentinoids has been reported to increase the risk of postoperative respiratory depression.⁴⁴ In contrast, there may be a beneficial effect of the combination of methadone and ketamine in the perioperative period. A synergistic antinociceptive effect of ketamine and methadone has been demonstrated in experimental neuropathy,⁴⁵ and the use of these agents together by patient-controlled analgesic administration has been shown to significantly decrease opioid consumption⁴⁶

Conclusions

Methadone is a long-acting opioid with a unique pharmacokinetic profile. It has additional central nervous system effects (NMDA receptor antagonism and inhibition of serotonin and norepinephrine uptake)⁹⁻¹⁴ that may enhance recovery by attenuating the development of hyperalgesia and tolerance and improve mood state. Randomized clinical trials in patients undergoing a variety of surgical procedures have documented that the use of methadone in the operating room is associated with significant reductions in postoperative analgesic requirements, compared to patients administered shorter-acting intraoperative opioids. In addition, most studies also demonstrated that pain scores were significantly lower in patients given methadone. The risk of opioid-related side effects was not increased in the methadone groups in any of the randomized clinical investigations.

For procedures associated with higher levels of postoperative pain (major spine or open abdominal or thoracic), a dose of 20 mg at induction of anesthesia has been demonstrated to provide long-lasting analgesia with a minimal risk of postoperative respiratory depression. Smaller doses (10 to 15 mg) have been administered in the elderly or those with limited physiologic reserve due to existent comorbidities.⁴ The careful titration of additional methadone in the PACU (3 to 5 mg with at least 20 min between doses) can further prolong the duration of postoperative analgesia. For procedures associated with moderate levels of postoperative pain (laparoscopic procedures), a dose of 10 mg before surgical incision will provide sufficient postoperative analgesia in most patients.

The majority of studies have used a single dose of methadone at induction of anesthesia and avoided the use of other intraoperative opioids. The investigation by Porter *et al.*¹⁶ documented that the administration of methadone before surgery was more effective in reducing postoperative analgesic requirements than a dose given at surgical closure. Furthermore, the peak respiratory depressant effect of methadone occurs approximately 8 to 10 min after administration.⁴ When an appropriate dose is given at induction of anesthesia, the peak respiratory depressant effect occurs at a time when the airway is controlled, and the duration of surgery will allow sufficient time for spontaneous recovery of ventilation. Due to the long half-life of methadone, there are limited data to suggest that repeat dosing is required in the operating room. If opioid-induced respiratory depression is suspected after the administration of methadone, a naloxone infusion may be required, and careful respiratory monitoring is indicated for the first 24 to 48 h.

The reasons why methadone is not more commonly administered to surgical patients (outside of complex spine surgery) are uncertain but may be related to misconceptions about pharmacokinetics and duration of action of the agent, concerns about prolonged respiratory depression after its administration, or limited published literature supporting its use in the perioperative setting. At the present time, the majority of investigations have been relatively small in size and should be considered “pilot studies.” Further, larger-scale, randomized trials are required to more clearly define the efficacy and safety of methadone use in the perioperative period. Data from such trials are needed before the routine use of methadone in surgical patients can be recommended. Optimal dosing regimens in various surgical procedures, as well as appropriate use in high-risk patient populations, has yet to be determined. In addition, the risk of postoperative respiratory depression, when compared to shorter-acting opioids, has not been definitively established. Finally, studies to determine the potential beneficial effects of a dose of intraoperative methadone on quality of recovery variables, bowel function, and hospital length of stay in enhanced recovery after surgery protocols, as well as the development of chronic postsurgical pain, are required.

Research Support

Supported by the Department of Anesthesiology, NorthShore University HealthSystem, Evanston, Illinois.

Competing Interests

Dr. Murphy has served on the Advisory Board and as a speaker for Merck (Kenilworth, New Jersey). Dr. Szokol declares no competing interests.

Correspondence

Address correspondence to Dr. Murphy: NorthShore University HealthSystem, 2650 Ridge Avenue, Evanston, Illinois 60201. dgmurphy2@yahoo.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

- Fletcher D, Fermanian C, Mardaye A, Aegerter P: Pain and Regional Anesthesia Committee of the French Anesthesia and Intensive Care Society (SFAR): A patient-based national survey on postoperative pain management in France reveals significant achievements and persistent challenges. *Pain* 2008; 137:441–51
- Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W: Pain intensity on the first day after surgery: A prospective cohort study comparing 179 surgical procedures. *ANESTHESIOLOGY* 2013; 118:934–44
- Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M: Enhanced recovery program in colorectal surgery: A meta-analysis of randomized controlled trials. *World J Surg* 2014; 38:1531–41
- Kharasch ED: Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration? *Anesth Analg* 2011; 112:13–6
- Mattick RP, Breen C, Kimber J, Davoli M: Methadone maintenance therapy *versus* no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009; 8:CD002209
- Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. *ANESTHESIOLOGY* 1982; 57:458–67
- Gourlay GK, Willis RJ, Wilson PR: Postoperative pain control with methadone: Influence of supplementary methadone doses and blood concentration–response relationships. *ANESTHESIOLOGY* 1984; 61:19–26
- Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM: Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. *Clin Pharmacol Ther* 1987; 41:392–401
- Davis AM, Inturrisi CE: D-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. *J Pharmacol Exp Ther* 1999; 289:1048–53
- Sotgiu ML, Valente M, Storchi R, Caramenti G, Biella GE: Cooperative N-methyl-D-aspartate (NMDA) receptor antagonism and μ -opioid receptor agonism mediate the methadone inhibition of the spinal neuron pain-related hyperactivity in a rat model of neuropathic pain. *Pharmacol Res* 2009; 60:284–90
- Zhao YL, Chen SR, Chen H, Pan HL: Chronic opioid potentiates presynaptic but impairs postsynaptic N-methyl-D-aspartic acid receptor activity in spinal cords: Implications for opioid hyperalgesia and tolerance. *J Biol Chem* 2012; 287:25073–85
- Richeb e P, Julien M, Brulotte V: Potential strategies for preventing chronic postoperative pain: A practical approach: Continuing Professional Development. *Can J Anaesth* 2015; 62:1329–41
- Codd EE, Shank RP, Schupsky JJ, Raffa RB: Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: Structural determinants and role in antinociception. *J Pharmacol Exp Ther* 1995; 274:1263–70
- Rojas-Corrales MO, Berrocoso E, Gibert-Rahola J, Mic o JA: Antidepressant-like effects of tramadol and other central analgesics with activity on monoamines reuptake, in helpless rats. *Life Sci* 2002; 72:143–52
- Gourlay GK, Willis RJ, Lamberty J: A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. *ANESTHESIOLOGY* 1986; 64:322–7
- Porter EJ, McQuay HJ, Bullingham RE, Weir L, Allen MC, Moore RA: Comparison of effects of intraoperative and postoperative methadone: Acute tolerance to the postoperative dose? *Br J Anaesth* 1983; 55:325–32
- Gottschalk A, Durieux ME, Nemergut EC: Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. *Anesth Analg* 2011; 112:218–23
- Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Vender JS, Benson J, Newmark RL: Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: A randomized, double-blinded, controlled trial. *ANESTHESIOLOGY* 2017; 126:822–33
- Sharma A, Tallchief D, Blood J, Kim T, London A, Kharasch ED: Perioperative pharmacokinetics of methadone in adolescents. *ANESTHESIOLOGY* 2011; 115:1153–61
- Stemland CJ, Witte J, Colquhoun DA, Durieux ME, Langman LJ, Balireddy R, Thammishetti S, Abel MF, Anderson BJ: The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. *Paediatr Anaesth* 2013; 23:51–7
- Chui PT, Gin T: A double-blind randomised trial comparing postoperative analgesia after perioperative

- loading doses of methadone or morphine. *Anaesth Intensive Care* 1992; 20:46–51
22. Richlin DM, Reuben SS: Postoperative pain control with methadone following lower abdominal surgery. *J Clin Anesth* 1991; 3:112–6
 23. Russell T, Mitchell C, Paech MJ, Pavy T: Efficacy and safety of intraoperative intravenous methadone during general anaesthesia for caesarean delivery: A retrospective case-control study. *Int J Obstet Anesth* 2013; 22:47–51
 24. Udelsmann A, Maciel FG, Servian DC, Reis E, de Azevedo TM, Melo Mde S: Methadone and morphine during anesthesia induction for cardiac surgery: Repercussion in postoperative analgesia and prevalence of nausea and vomiting. *Rev Bras Anesthesiol* 2011; 61:695–701
 25. Carvalho AC, Sebold FJG, Calegari PMG, Oliveira BH, Schuelter-Trevisol F: [Comparison of postoperative analgesia with methadone *versus* morphine in cardiac surgery]. *Rev Bras Anesthesiol* 2018; 68:122–7
 26. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Shear T, Parikh KN, Patel SS, Gupta DK: Intraoperative methadone for the prevention of postoperative pain: A randomized, double-blinded clinical trial in cardiac surgical patients. *ANESTHESIOLOGY* 2015; 122:1112–22
 27. Simoni RE, Cangiani LM, Pereira AM, Abreu MP, Cangiani LH, Zemi G: [Efficacy of intraoperative methadone and clonidine in pain control in the immediate postoperative period after the use of remifentanyl]. *Rev Bras Anesthesiol* 2009; 59:421–30
 28. Rivosecchi RM, Rice MJ, Smithburger PL, Buckley MS, Coons JC, Kane-Gill SL: An evidence based systematic review of remifentanyl associated opioid-induced hyperalgesia. *Expert Opin Drug Saf* 2014; 13:587–603
 29. Komen H, Brunt LM, Deych E, Blood J, Kharasch ED: Intraoperative methadone in same-day ambulatory surgery: A randomized, double-blinded, dose-finding pilot study. *Anesth Analg* 2019; 128:802–10
 30. Berde CB, Beyer JE, Bournaki MC, Levin CR, Sethna NF: Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; 119:136–41
 31. Singhal NR, Jones J, Semenova J, Williamson A, McCollum K, Tong D, Jerman J, Notrica DM, Nguyen H: Multimodal anesthesia with the addition of methadone is superior to epidural analgesia: A retrospective comparison of intraoperative anesthetic techniques and pain management for 124 pediatric patients undergoing the Nuss procedure. *J Pediatr Surg* 2016; 51:612–6
 32. Norris JV, Don HF: Prolonged depression of respiratory rate following methadone analgesia. *ANESTHESIOLOGY* 1976; 45:361–2
 33. Dunn LK, Yerra S, Fang S, Hanak MF, Leibowitz MK, Alpert SB, Tsang S, Durieux ME, Nemergut EC, Naik BI: Safety profile of intraoperative methadone for analgesia after major spine surgery: An observational study of 1,478 patients. *J Opioid Manag* 2018; 14:83–7
 34. Baldo BA: Opioid analgesic drugs and serotonin toxicity (syndrome): Mechanisms, animal models, and links to clinical effects. *Arch Toxicol* 2018; 92:2457–73
 35. Kharasch ED, Regina KJ, Blood J, Friedel C: Methadone pharmacogenetics: CYP2B6 polymorphisms determine plasma concentrations, clearance, and metabolism. *ANESTHESIOLOGY* 2015; 123:1142–53
 36. Cozowicz C, Chung F, Doufas AG, Nagappa M, Memtsoudis SG: Opioids for acute pain management in patients with obstructive sleep apnea: A systematic review. *Anesth Analg* 2018; 127:988–1001
 37. Alinejad S, Kazemi T, Zamani N, Hoffman RS, Mehrpour O: A systematic review of the cardiotoxicity of methadone. *EXCLI J* 2015; 14:577–600
 38. Johnston J, Pal S, Nagele P: Perioperative torsade de pointes: A systematic review of published case reports. *Anesth Analg* 2013; 117:559–64
 39. Nagele P, Pal S, Brown F, Blood J, Miller JP, Johnston J: Postoperative QT interval prolongation in patients undergoing noncardiac surgery under general anesthesia. *ANESTHESIOLOGY* 2012; 117:321–8
 40. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006; 367:1618–25
 41. Moyses DW, Kaye AD, Diaz JH, Qadri MY, Lindsay D, Pyati S: Perioperative ketamine administration for thoracotomy pain. *Pain Physician* 2017; 20:173–84
 42. McNicol ED, Schumann R, Haroutounian S: A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014; 58:1199–213
 43. Muhly WT, Sankar WN, Ryan K, Norton A, Maxwell LG, DiMaggio T, Farrell S, Hughes R, Gornitzky A, Keren R, McCloskey JJ, Flynn JM: Rapid recovery pathway after spinal fusion for idiopathic scoliosis. *Pediatrics* 2016; 137:e20151568
 44. Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN: Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression. *Anesth Analg* 2017; 125:141–6
 45. Pelissier T, Laurido C, Kramer V, Hernández A, Paeile C: Antinociceptive interactions of ketamine with morphine or methadone in mononeuropathic rats. *Eur J Pharmacol* 2003; 477:23–8
 46. Pacreu S, Fernández Candil J, Moltó L, Carazo J, Fernández Galinski S: The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. *Acta Anaesthesiol Scand* 2012; 56:1250–6