Intraoperative Methadone in Same-Day Ambulatory Surgery: A Randomized, Double-Blinded, Dose-Finding Pilot Study

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BACKGROUND: Approximately 50 million US patients undergo ambulatory surgery annually. Postoperative opioid overprescribing is problematic, yet many patients report inadequate pain relief. In major inpatient surgery, intraoperative single-dose methadone produces better analgesia and reduces opioid use compared with conventional repeated dosing of short-duration opioids. This investigation tested the hypothesis that in same-day ambulatory surgery, intraoperative methadone, compared with short-duration opioids, reduces opioid consumption and pain, and determined an effective intraoperative induction dose of methadone for same-day ambulatory surgery.
METHODS: A double-blind, dose-escalation protocol randomized 60 patients (2:1) to intraoperative single-dose intravenous methadone (initially 0.1 then 0.15 mg/kg ideal body weight) or conventional as-needed dosing of short-duration opioids (eg, fentanyl, hydromorphone; controls). Intraoperative and postoperative opioid consumption, pain, and opioid side effects were assessed before discharge. Patient home diaries recorded pain, opioid use, and opioid side effects daily for 30 days postoperatively. Primary outcome was in-hospital (intraoperative and postoperative) opioid use. Secondary outcomes were 30 days opioid consumption, pain intensity, and opioid side effects.
RESULTS: Median (interquartile range) methadone doses were 6 (5–6) and 9 (8–9) mg in the 0.1 and 0.15 mg/kg methadone groups, respectively. Total opioid consumption (morphine equivalents) in the postanesthesia care unit was significantly less compared with controls (9.3 mg, 1.3–11.0) in subjects receiving 0.15 mg/kg methadone (0.1 mg, 0.1–3.3; $P < .001$) but not 0.1 mg/kg methadone (5.0 mg, 3.3–8.1; $P = .60$). Dose-escalation ended at 0.15 mg/kg methadone. Total in-hospital nonmethadone opioid use after short-duration opioid, 0.1 mg/kg methadone, and 0.15 mg/kg methadone was 35.3 (25.0–44.0), 7.1 (3.7–10.0), and 3.3 (0.1–5.8) mg morphine equivalents, respectively ($P < .001$ for both versus control). In-hospital pain scores and side effects were not different between groups. In the 30 days after discharge, patients who received methadone 0.15 mg/kg had less pain at rest ($P = .02$) and used fewer opioid pills than controls ($P < .0001$), whereas patients who received 0.1 mg/kg had no difference in pain at rest ($P = .69$) and opioid use compared to controls ($P = .08$).
CONCLUSIONS: In same-day discharge surgery, this pilot study identified a single intraoperative dose of methadone (0.15 mg/kg ideal body weight), which decreased intraoperative and postoperative opioid requirements and postoperative pain, compared with conventional intermittent short-duration opioids, with similar side effects. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Can an optimal single intraoperative dose of methadone provide adequate analgesia, and reduce opioid consumption, compared with conventional repetitive dosing of short-duration opioids, for same-day discharge ambulatory surgery?
- **Findings:** In a dose-escalation dose-finding pilot study, a single induction dose of methadone (0.15 mg/kg ideal body weight) decreased intraoperative and postoperative opioid requirements and reduced postoperative pain.
- **Meaning:** Pilot findings suggest that single-dose intraoperative methadone may be useful for same-day discharge ambulatory surgery.

Surgical patients expect adequate pain relief with minimal or no adverse side effects.[1] More than 80% report inadequately treated postoperative pain,[2,3] which can cause increased morbidity and mortality and risk of chronic postsurgical pain that develops in 10%–50% of patients.[4,5] Acute postoperative pain is the single greatest risk factor for chronic postsurgical pain.[4,6,7]

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Opioids are the primary pharmacotherapy for moderate to severe surgical pain. Use of shorter-duration opioids has increased in the past 2 decades,[8] but has not improved surgical pain treatment.[2] Opioid-related side effects, like respiratory depression, continue to complicate postoperative pain treatment.[9–11]

In contrast to conventional use of intraoperative short-duration opioids (fentanyl and congeners, morphine, hydromorphone), a single dose of a long-duration opioid (ie, methadone) produces better analgesia than repeated doses of short-duration opioids.[12] This has been shown repeatedly in inpatients undergoing major surgery.[13–21] Methadone is a μ-opioid agonist with several advantages compared with commonly used opioids, including rapid onset of effect, absence of active metabolites, and long elimination half-life (1–2 days), and is also an *N*-methyl-D-aspartate receptor antagonist.[12,22,23] The long methadone elimination half-life results in prolonged effect and significantly diminished need for postoperative analgesics.[12]

Nevertheless, methadone in outpatient surgery has not been evaluated. The appropriate dose in same-day ambulatory surgery has also not been defined. Short- and longer-term effects on opioid consumption, pain, and potential side effects are unknown.

The objective of this pilot study was to determine the clinical effectiveness of intraoperative single-dose methadone in same-day discharge ambulatory surgery and to determine an effective dose for these surgical procedures. The primary aim was to examine intraoperative and postoperative opioid utilization until discharge from the hospital. Secondary aims were to compare single-dose methadone versus conventional use of short-duration opioids with respect to 30-day postoperative opioid consumption, immediate (predischarge), and 30-day postoperative pain intensity and pain relief; and postoperative opioid side effects. Because methadone anesthesia for outpatient surgery had not previously been studied, this investigation was conducted as a dose-finding pilot study using escalating dose groups to determine an optimal methadone dose.

METHODS

Protocol

This investigation was a single-center, randomized, double-blind, parallel-group, dose-escalation, dose-finding pilot. The protocol and consent document were approved by the Washington University in St Louis Institutional Review Board and the investigation was registered at clinicaltrials.gov (NCT02300077, principal investigator: Helga Komen, date of registration: November 18, 2014), before patient enrollment. All patients provided written informed consent. This manuscript adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. Potential participants were identified by investigators and research coordinators from operating room schedules. Inclusion criteria were patients 18–65 years of age, undergoing elective same-day discharge ambulatory surgery under general anesthesia. Exclusion criteria included a history of liver or kidney disease, pregnant or nursing females, and potentially opioid-tolerant patients (ie, daily use of methadone, >20 mg/day oxycodone or hydrocodone, or fentanyl transdermal patch). Patients were typically undergoing laparoscopic cholecystectomy, tubal ligation, or salpingectomy and/or oophorectomy, and were enrolled between March 2015 and May 2016.

Before surgery, patients were asked to complete a short questionnaire regarding the past 7 days average pain intensity and pain interference, as well as overall physical-mental health and expected level of postoperative pain (based on NIH PROMIS-29 Profile v2.0, Patient Reported Outcomes Measurement Information System). Demographic data were recorded.

Patients were assigned sequential study numbers and were randomized by blocks of 3 using a published randomization table, in a 2:1 ratio (methadone:control), to receive either intraoperative single-dose methadone or conventional practice (intraoperative short-duration opioid; fentanyl, sufentanil, hydromorphone, or morphine, with drug choice and dosing at practitioners' discretion). The initial cohort of 20 methadone patients received 0.1 mg/kg ideal body weight, and the second cohort received 0.15 mg/kg ideal body weight (dose rounded to the nearest 0.5 mg). The anesthesia provider was given a numbered sealed envelope, prepared by an otherwise uninvolved individual, containing the randomization assignment. The investigators, patients, and research staff evaluating the patients were blinded to drug group assignment. The anesthesia provider and postanesthesia care unit (PACU) nurses were unblinded. PACU staff were unaware of the study objectives, design, and outcomes. Anesthesia and surgical care were not altered for study purposes, except that patients in the methadone groups received methadone as their intraoperative opioid, rather than leaving the choice and doses of intraoperative opioid to the provider, and no one in the control (short-duration opioid) group received methadone.

Patient premedication was at the discretion of the anesthesia care team. Anesthetic induction was with propofol or etomidate and muscle relaxant at the anesthesia provider's discretion, and the designated opioid (single-dose methadone or unrestricted short-duration opioids). The opioid could be given in the operating room up to 5–10 minutes before the propofol or etomidate. Anesthetic maintenance was with volatile anesthetic (sevoflurane or desflurane) or propofol at the anesthesia provider's discretion. Patients receiving methadone at induction received no additional opioid during the surgical procedure. Patients randomized to receive short-duration opioids could receive additional doses of fentanyl, sufentanil, morphine, or hydromorphone during maintenance at the provider's discretion. To ensure patient comfort, at the end of the procedure, during wound closure or after emergence, additional opioid could be given for pain, in all groups. Patients in both methadone and short-duration opioid groups received only fentanyl, morphine, or hydromorphone during emergence. Less commonly and more variably used drugs (nitrous oxide, ketamine, dexmedetomidine) were generally avoided, to reduce variability. Antiemetic prophylaxis (ondansetron, 4 mg intravenous) was given per usual practice to each patient toward the end of surgery.

Postoperative care and analgesia were per institutional practice, and not altered for study purposes. In the PACU, patients could receive fentanyl or hydromorphone, with dosing (for mild, moderate, or severe pain) based on patient pain reports on a 0–10 verbal scale (1–3, 4–6, or 7–10, respectively), per institutional standing orders and standard practice. Additional antiemetic (ondansetron) or

diphenhydramine was given if needed. Additional oral analgesics (oxycodone, hydrocodone, or acetaminophen) after discharge from the PACU and until discharge from the hospital, if needed, were prescribed by the surgical team. Postdischarge opioids were prescribed by the surgical team. These included oxycodone (5 mg), oxycodone (5 mg)/acetaminophen (325 mg), and hydrocodone (5 mg)/acetaminophen (325 mg).

Postoperatively, patients were assessed for pain, sedation, and pain relief satisfaction after PACU admission, every 15 minutes for the first hour, hourly for the next 4 hours, and before discharge. All assessments were conducted by a trained member of the research team, blinded to randomization allocation. We used a standard protocol for assessment of pain intensity (at rest, with coughing, and with activity) using a 0–10 Numeric Rating Scale. Observed sedation (Modified Observer's Assessment of Alertness/Sedation: MOAA/S, 0–5),[24] was recorded concurrently with pain assessments. During PACU recovery, adverse events were recorded: respiratory depression (respiratory rate <8/min), reintubation, decreased oxygen saturation (<90% for >1 minute; <85% for >30 seconds), excessive sedation (MOAA/S, 0–2), pain/sedation mismatch (defined as MOAA/S, 0–2 and pain score >5[10]). Drug administration for prophylaxis/treatment of opioid side effects (eg, antiemetics) was recorded from our electronic medical record system. Opioid side effects were assessed before discharge using the Opioid-Related Symptom Distress Scale (ORSDS). ORSDS uses 4-point Likert scales to characterize 12 opioid side effects (nausea, vomiting, constipation, difficulty urinating, difficulty concentrating, drowsiness, dizziness, confusion, fatigue, itching, dry mouth, and headache) according to frequency, severity, and bothersomeness.

For the 30-day postoperative follow-up, patients were given a paper diary to record their average pain for that day (at rest, with activity, with coughing; using a 0–10 numerical rating scale). They also recorded pain interference with 7 activities of daily living (mood, ability to walk or move, sleep, normal work outside the home, normal work at home, recreational activities, and enjoyment of life, on a 5-point Likert scale). Questions were based on the Patient Reported Outcomes Measurement Information System Pain Behavior and Pain Interference item banks. Patients also recorded opioid and nonopioid analgesic use, sedation, and time to return to work. Opioid side effects (ORSDS) were assessed 7, 14, and 30 days postoperatively. Patients were also asked about the number of remaining pain medication pills and their disposal at the 30-day time point.

Data and Statistical Analysis

The dose-finding nature of the protocol required interim assessments after each methadone dose cohort. Methadone dose-escalation ceased when subjects required minimal PACU opioid defined as opioid dose given in the PACU that was lower than the one given in control patients (without increased adverse events), and the protocol was then completed per plan, and cumulative data were analyzed.

The primary outcome was in-hospital opioid utilization (intraoperative and postoperative). A secondary outcome was 30-day postoperative opioid consumption. All opioid dosing was converted to intravenous morphine equivalents for analysis.[25] Additional secondary outcomes included in-hospital postoperative pain scores and pain relief scores, 30-day postdischarge pain scores, in-hospital, and 30-day postdischarge opioid side effects. Because this was a dose-escalation study, there was a planned partial analysis of predischarge nonmethadone opioid requirement after each methadone dose cohort was completed. The sample size for this pilot investigation was based on previous studies.[26] All outcomes were compared for statistical significance between methadone and short-duration opioid groups, univariable at each time point and multivariable using repeated measures models. All outcomes were assessed visually to select appropriate statistical distributions for the analysis. For univariate analysis of categorical outcomes comparing groups, χ^2 or Fisher exact test was used, as appropriate, depending on expected counts. For continuous variables, the Kruskal-Wallis test was used to compare groups. Initially, the univariate analyses were performed comparing multiple groups simultaneously. For the outcomes with a significant difference among groups, we additionally compared all group pairs, adjusting for multiple testing using the Bonferroni method. ORSDS was first analyzed by symptom for frequency (% of patients affected), and then, if there were significant differences between groups, for bothersomeness.

For repeated measures analysis, generalized linear mixed model analysis was used, adjusting for time and accounting for within-patient correlation. For binary outcomes, such as symptom presence, nonlinear logistic mixed effects models with binomial distribution were used. For outcomes such as numerical rating scales with excessive number of zero scores, each time point was modeled separately using a zero-inflated negative binomial model. For count outcomes, such as number of symptoms, a Poisson distribution was assumed. For continuous outcomes, such as dose, the data were log-transformed before linear mixed effects models analysis was done. In addition, we used survival log-rank tests and Kaplan-Meier plots to assess time to discontinuation of symptoms or opioids and time to alertness. For outcomes on the ordinal scale, such as symptom intensity, cumulative logit models were used. Sedation levels were compared using a repeated measures model with binomial link, adjusting for time and within-patient correlation. The analysis was also performed without binarizing MOASS, with a Poisson model. In addition, data were analyzed with a time to event (alertness of 5 or 4) model. For all analyses, P values <.05 were considered statistically significant. R software version 3.3.1 was used for all analyses.

Normally distributed data are presented as the mean ± standard deviation, and nonnormally distributed data are presented as the median and interquartile range (IQR).

RESULTS

A total of 156 patients were screened for inclusion. Of these, 86 were not eligible or did not consent. Among 70 patients who consented, 4 were withdrawn from the study for additional reasons (liver/kidney disease, n = 2; consent withdrawn by patient, n = 1; anesthesia provider refused participation, n = 1), leaving 66 patients for randomization (Figure 1). After randomization, 6 patients were excluded

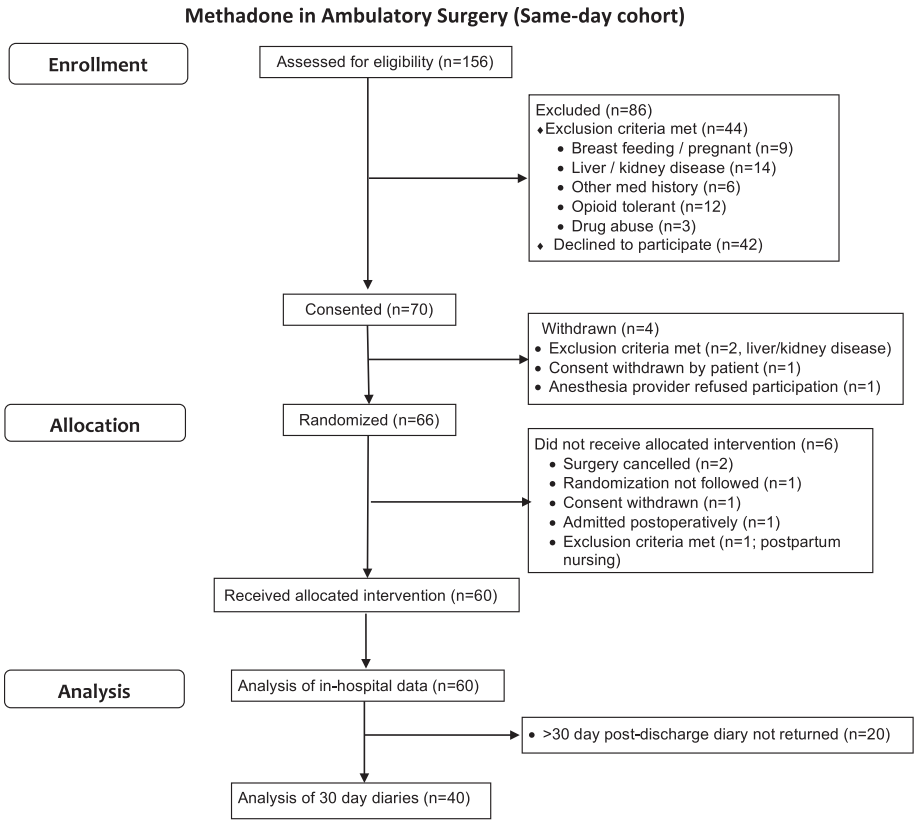

Figure 1. CONSORT flow diagram for screening, inclusion, and exclusion of trial participants. CONSORT indicates Consolidated Standards of Reporting Trials.

because of canceled surgery, randomization not followed, change in surgical plan (ie, postoperative admission), withdrawal of consent, and violation of exclusion criteria (after enrollment and randomization a patient disclosed she was lactating). Data from 60 patients were analyzed for the in-hospital portion of the study. Postoperative 30-day diaries were returned by 40 patients. The trial ended once the planned number of patients was enrolled, and analysis confirmed the effectiveness of the methadone dose.

Demographic data and anesthetic characteristics were similar in the 3 groups with respect to age, body weight, ideal body weight, American Society of Anesthesiologists physical status, anesthesia duration, and types of surgeries (Table 1). Ten and 11 controls were enrolled contemporaneously with the 0.1 and 0.15 mg/kg methadone groups, respectively. As expected, there was less overall interindividual variability in ideal body weight (13%) than actual body weight (32%).

Median intraoperative methadone doses were 6 and 9 mg in the 0.1 and 0.15 mg/kg ideal body weight groups, respectively (Table 1). There was little within-group variation in methadone dose, because of dosing to ideal body weight. In the controls, all patients received either fentanyl or fentanyl and hydromorphone (11 and 10 patients, respectively). Median (IQR) doses were 250 μg (200–250) fentanyl and 0 mg (0–0.75) hydromorphone. No patient received sufentanil or morphine.

Opioid consumption before hospital discharge is shown in Table 2. Median differences are shown in Supplemental Digital Content, Table 1, http://links.lww.com/AA/C411. The determinant of methadone dose escalation was PACU opioid requirement. Total PACU opioid consumption in subjects receiving conventional dosing of short-duration opioids was 9.3 mg morphine equivalents (IQR, 1.3–11.0 mg). It was not lower in subjects receiving 0.1 mg/kg methadone (5.0 mg, 3.3–8.1; $P = .60$) versus controls, so the methadone dose was escalated. PACU opioid consumption was significantly lower and minimal (0.1 mg, 0.1–3.3) in subjects receiving 0.15 mg/kg methadone ($P < .0001$), and the null hypothesis was rejected. This was considered an effective dose, and enrollment was completed at this dose cohort.

The primary outcome measure was postoperative opioid utilization until discharge from the hospital. In patients receiving 0.1 mg/kg methadone, compared with controls, total intraoperative nonmethadone opioid requirements were significantly less, but total PACU opioid requirements, total day of surgery nonoperating room (OR) (PACU + post-PACU) nonmethadone opioid requirements, and the number of patients needing no additional PACU opioid were not different. Therefore, the dose of methadone was escalated to 0.15 mg/kg ideal body weight and additional patients studied (with additional randomized controls). In patients receiving 0.15 mg/kg methadone, total intraoperative nonmethadone opioid requirements, total PACU opioid requirements, and total day of surgery non-OR (PACU + post-PACU) nonmethadone opioid requirements were significantly less, and more patients needed no additional PACU opioid, compared with controls receiving short-duration opioids, and compared with 0.1 mg/kg methadone. Therefore, higher methadone doses were not evaluated.

Several secondary outcomes were evaluated before hospital discharge. Postoperative pain was assessed by numeric

Table 1. Demographic Data and Anesthetic Characteristics

	Control (Short-Duration Opioid)	Methadone 0.1 mg/kg IBW	Methadone 0.15 mg/kg IBW
Number of patients	21	18	21
Age (y)	42 ± 13	37 ± 11	40 ± 11
sex (M:F)	3:18	2:16	0:21
Race/ethnicity			
Caucasian	13 (62)	15 (83)	12 (57)
African-America	7 (33)	3 (17)	9 (43)
Asian	1 (5)	0 (0)	0 (0)
Actual weight (kg)	85 ± 16	88 ± 42	86 ± 26
IBW (kg)	60 ± 5	57 ± 6	57 ± 6
ASA physical status, n (%)			
I	1 (5)	0 (0)	0 (0)
II	16 (76)	17 (94)	21 (100)
III	4 (19)	1 (6)	0 (0)
Anesthesia duration (min)	86 ± 21	102 ± 17	84 ± 22
Surgery			
Laparoscopic cholecystectomy	11	11	5
Laparoscopic tubal ligation	6	1	7
Laparoscopic salpingectomy ± oophorectomy	2	6	9
Laparoscopic inguinal hernia repair	2	0	0
Intraoperative methadone (mg)	0	5.5 (5.0–6.0)	8.5 (7.8–9.0)
Ready for PACU discharge (min)	96 ± 50	94 ± 45	128 ± 106

Results are the mean ± standard deviation.
Abbreviations: ASA, American Society of Anesthesiologists; IBW, ideal body weight; PACU, postanesthesia care unit.

Table 2. In-Hospital Opioid Consumption

	Control (Short-Duration Opioid)	Methadone 0.1 mg/kg IBW	*P* Value Versus Control	Methadone 0.15 mg/kg IBW	*P* Value Versus Control
Primary outcomes					
Total intraoperative nonmethadone opioid (mg morphine equivalents)	25.0 (23.3–28.3)	0.1 (0.1–0.1)	<.0001	0.1 (0.1–0.1)	<.0001
Total PACU nonmethadone opioid (mg morphine equivalents)	9.3 (1.3–11.0)	5.0 (3.3–8.1)	.60	0.1 (0.1–3.3)	<.0001
Number of patients (%) needing no PACU opioid	5 (24%)	2 (11%)	.42	12 (57%)	.06
Total post-PACU nonmethadone opioid (mg morphine equivalents)	0.0 (0.0–2.9)	0.0 (0.0–0.6)	.19	0.0 (0.0–2.5)	.79
Total day of surgery non-OR (PACU + post-PACU) total nonmethadone opioid (mg morphine equivalents)	10.0 (2.5–14.3)	5.4 (3.3–9.6)	.42	3.3 (0.1–5.8)	.01
Total day of surgery nonmethadone opioid (mg morphine equivalents)	35.3 (25.0–44.0)	7.1 (3.7–10.0)	<.0001	3.3 (0.1–5.8)	<.0001
Total day of surgery opioid (mg morphine equivalents)	35.3 (25.0–44.0)	13.3 (8.9–16.4)	<.0001	12.3 (8.9–14.3)	<.0001

Results are the median (interquartile range).
Abbreviations: IBW, ideal body weight; OR, operating room; PACU, postanesthesia care unit.

rating scale scores in 15-minute increments for the first hour in the PACU, and hourly thereafter up to 4 hours or until discharge (Figure 2A). There was no significant difference between the 3 groups in pain scores at rest, with coughing, with activity (P = .177). There was also no significant difference between groups at any individual time point (P values between 0.325 and 0.967). There was also no influence of methadone on the day of surgery sedation (P = .96, Figure 2B), and no instance of excessive sedation (MOAA/S 0–2) occurred in any patient. There were no adverse respiratory events (respiratory rate <8, oxygen saturation <90% for >1 minute, reintubation, pain/sedation mismatch) in any patient. There was no significant difference between groups in PACU drug administration to treat nausea or emesis. The number or percentage of patients receiving PACU ondansetron (6, 4, and 6, respectively), PACU diphenhydramine (3, 1, and 1), or any PACU antiemetic (43%, 28%, and 33%) in the control, 0.1 mg/kg methadone, and 0.15 mg/kg methadone groups was not different (P = .60). Time to readiness for PACU discharge, as recorded by PACU nurses, was not different in patients receiving methadone versus short-duration opioids (Table 1). There were no differences between control and either methadone group regarding in-hospital opioid-related adverse symptoms (Table 3).

Several secondary outcomes were evaluated after hospital discharge, based on 30-day take-home diaries. Pain at rest was significantly less than controls in patients receiving methadone 0.15 mg/kg (P = .02), but not methadone 0.1 mg/kg (P = .69) (Figure 2C). There was no significant difference between groups in pain with activity (P = .191) or pain with coughing (P = .116; not shown), or time to first pain-free day (not shown). There was no significant difference between groups in mood (P = .23), ability to walk or move (P = .31), sleep (P = .25), normal work outside the home

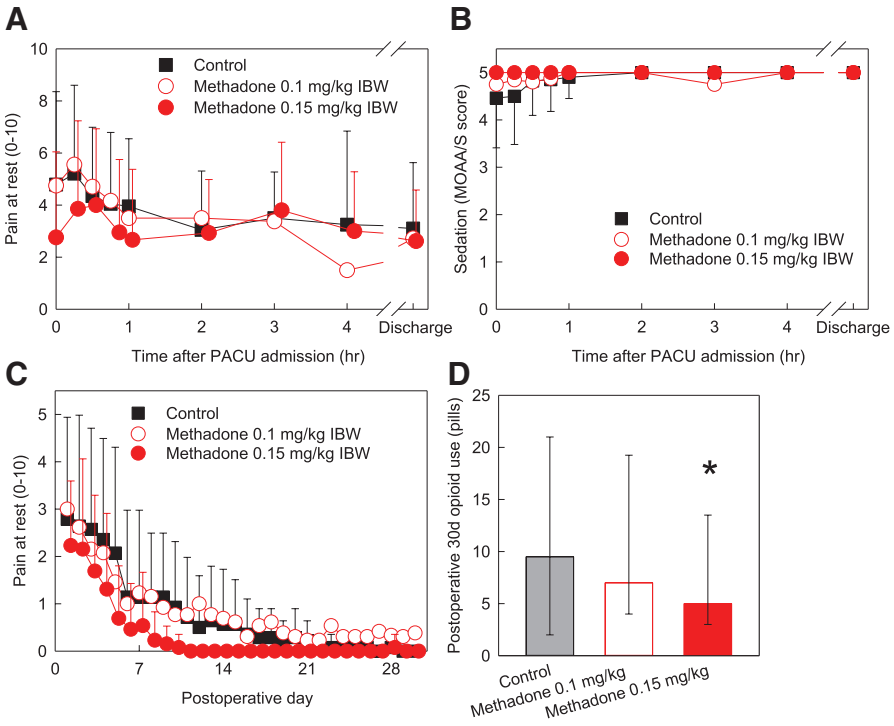

Figure 2. Clinical outcomes. A, Postoperative pain at rest. Patients were asked to rate their pain on a 0–10 numeric rating scale. Results are the mean ± standard deviation (SD). Some SDs are omitted for clarity. B, Day of surgery postoperative sedation. Sedation was scored (0 = unresponsive, 5 = awake) using the Modified Observer's Assessment of Alertness/Sedation. Results are the mean ± SD. Some SDs are omitted for clarity. C, Postdischarge pain at rest. Patients rated their pain on a 0–10 numeric rating scale. Pain at rest was significantly less than controls in patients receiving methadone 0.15 mg/kg ($P = .02$) but not methadone 0.1 mg/kg ($P = .69$). D, Postdischarge opioid consumption. Results are cumulative 30 days postdischarge opioid pills consumed. Results are the median and interquartile range. *$P < .0001$ compared with control (short-duration opioids). IBW indicates ideal body weight; PACU, postanesthesia care unit.

Table 3. Day of Surgery Opioid-Related Symptoms (ORSDS, at Discharge)

Symptom	Control (% of Patients)	Methadone 0.10 mg/kg (% of Patients)	Methadone 0.15 mg/kg (% of Patients)	*P* Value
Nausea	33	33	48	.67
Vomiting	5	0	10	.77
Difficulty passing urine	5	11	5	.67
Difficulty concentrating	19	22	5	.28
Drowsiness, difficulty staying awake	67	56	48	.44
Feeling lightheaded or dizzy	33	33	24	.82
Feeling confused	5	6	0	.75
Fatigue	71	67	67	1.00
Itchiness	24	11	19	.64
Dry mouth	86	72	81	.66
Headache	19	6	5	.35

Abbreviation: ORSDS, Opioid-Related Symptom Distress Scale.

($P = .82$), normal work at home ($P = .47$), recreational activities ($P = .14$), and enjoyment of life ($P = .20$).

Postoperative take-home opioids were prescribed by surgeons. The most common opioids were oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 5 mg/acetaminophen 325 mg. Postdischarge 30-day opioid consumption based on take-home diaries is shown in Table 4. The time to discontinue opioid use was not different between cholecystectomy and salpingectomy/oophorectomy, and tubal ligation ($P = .174$). Compared with controls, there were significantly fewer opioid pills used in patients receiving methadone 0.15 mg/kg ($P < .0001$) but not 0.1 mg/kg ($P = .087$), and there was a significant difference between methadone doses ($P = .019$; Figure 2D). Results were similar when calculated as morphine equivalents (not shown). The total number of patients using ≤10 and ≤5 pills was 26 and 15, respectively. The fraction of patients using ≤10 and ≤5 pills in the methadone groups was not significantly different ($P = .23$) from controls. There was no difference in the time to first opioid-free day between the 3 groups (not shown). Time to opioid discontinuation was significantly less than controls in the 0.1 mg/kg methadone group ($P = .02$) but not the 0.15 mg/kg methadone group (not shown).

Opioid-related symptoms were examined at 7, 14, and 30 days postdischarge. Nausea was reported in some patients on all 3 days; no vomiting was reported on days 14 and 30. Groups were compared by symptoms of nausea at each of the 3 days and by vomiting at day 7. A repeated measures model for nausea was also fit, with binomial distribution, adjusting for within-patient correlation. No significant difference in nausea and vomiting between groups was found at any time point. In a repeated measures model adjusting for time, the 0.1 mg/kg methadone group reported significantly more nausea than controls ($P < .001$).

Among all patients, a median of 30 opioid pills were prescribed per patient (IQR, 22–40; minimum–maximum, 5–70), representing 1820 pills dispensed. In the 40 patients returning the 30-day diaries, a median of 8 opioid pills was consumed per patient (IQR, 3–18; range 0–33), representing a total of 428 pills consumed, and 928 were left over unused (median 23 per patient; IQR, 17–30). Ninety-five percent of patients had leftover unused opioids.

DISCUSSION

Intraoperative single-dose methadone administration for inpatient surgery (orthopedic, spine, abdominal, and cardiac) in adults and children has been previously described.[13–21,26] For these operations, in adults, methadone

Table 4. Postdischarge Opioid Consumption

	Control (Short-Duration Opioid) (n = 14)	Methadone 0.1 mg/kg IBW (n = 13)	*P* Value Versus Control	Methadone 0.15 mg/kg IBW (n = 12)	*P* Value Versus Control
Number of opioid pills prescribed	30 (20–45)	30 (30–40)		30 (23–30)	
Total postdischarge opioid pills used	10 (3–20)	7 (4–19)	.087	5 (3–13)	<.001
Number of patients using ≤10 pills	8 (57%)	9 (69%)	.70	9 (75%)	.43
Number of patients using ≤5 pills	4 (29%)	4 (31%)	1.0	7 (58%)	.23
Number of unused opioid pills	26 (7–34)	23 (20–30)	.79	22 (14–29)	.93

Results are based on 30-day postoperative diaries. Not all patients returned the diary.
Results are the median (interquartile range).
Abbreviation: IBW, ideal body weight.

doses at anesthetic induction were originally 20 mg,[13–15,17] and later 0.2,[19,21] 0.25,[18] and 0.3 mg/kg.[20] Only 1 instance of methadone use (routine 10 mg oral methadone, or 5 mg in patients >60 years, immediately before surgery) in same-day ambulatory surgery has been reported.[27]

This pilot study determined an effective dose of intraoperative single-dose methadone in same-day discharge ambulatory surgery patients. Patients underwent elective, moderately painful procedures, including laparoscopic cholecystectomy, tubal ligation, salpingectomy, and/or oophorectomy. Because the optimal methadone dose in these operations was unknown, and owing to patient safety considerations, the protocol used a dose-escalation design, with 0.1 mg/kg starting dose and 0.05 mg/kg increments. An effective dose was defined as one that minimized pain and PACU opioid requirement, without untoward side effects. The goal was not to increase the dose further, to find a maximally tolerable dose, as that would have caused unwanted side effects.

Results showed that intravenous methadone 0.15 mg/kg ideal body weight (median 9 mg) but not 0.10 mg/kg (median 6 mg) at induction significantly reduced requirements for additional intraoperative and postoperative (PACU) opioid, compared with conventional anesthesia practice using intermittent short-duration opioids. After median 9 mg methadone in these outpatients, PACU opioid requirement averaged <1 mg morphine equivalent. Because of obesity, weight-based dosing can confuse practitioners as to whether actual weight or ideal body weight should be used. To minimize interpatient variability in dose, this investigation used ideal body weight.[28] The range of actual methadone doses was consequently small. Methadone was not associated with a higher incidence of adverse effects (sedation, nausea, emesis, respiratory depression) or delayed PACU discharge. Total median day of surgery opioid (OR, PACU, post-PACU) in patients receiving methadone 0.15 mg/kg was 12.3 (8.9–14.3) mg morphine equivalents. Further studies in comparable patient populations undergoing similar procedures might receive a single 10 mg intravenous methadone dose at induction, for simplicity.

Results in same-day discharge outpatients are similar to results in inpatients undergoing major surgery. An early report of methadone (20 vs 20 mg morphine) at induction in patients undergoing upper abdominal incision found lower postoperative opioid requirements after methadone (12 ± 8 vs 41 ± 14 mg).[15] Abdominal hysterectomy patients needed less 72-hour postoperative opioid after 20 mg intraoperative methadone than 20 mg morphine (average 6 vs 46 mg).[17] In complex spine surgery, patients receiving intraoperative methadone (0.2 mg/kg) versus sufentanil infusion had 50% lower postoperative opioid requirements.[19] In spinal fusion, methadone (0.2 mg/kg) compared with hydromorphone reduced total 72 hours postoperative opioid requirements.[21] In cardiac surgery, intraoperative methadone (0.3 mg/kg) compared with fentanyl reduced total 72 hours postoperative opioid requirements.[20] Patients receiving methadone also reported lower pain intensity and improvements in self-perceived quality of pain management.[17,19–21]

Several secondary outcomes also showed significant differences between patients receiving methadone compared with short-duration opioids. Pain at rest in the 30-day postoperative period was less after methadone 0.15 mg/kg administration, although more provoked pain (with activity and coughing) was not different. The total number of opioid pills and morphine mg equivalents was significantly less in patients receiving methadone 0.15 mg/kg compared with conventional short-duration intraoperative opioids. This could suggest a need for fewer discharge opioid pills prescribed in ambulatory surgery patients.

The provision of satisfactory and safe pain relief is no less important in ambulatory than inpatient surgery. Ambulatory surgery constitutes >60% of surgical procedures performed in the United States.[29] These are a substantial fraction of the more than 310 million procedures performed annually worldwide.[30] Patients report unexpectedly high levels of pain after seemingly "minor" surgical procedures, including laparoscopic appendectomy, cholecystectomy, and salpingo-oophorectomy.[31] While commonly believed that laparoscopic procedures are minimally or less painful than their open counterparts, worst pain ratings (0–10 numerical rating scale) were only 0.5–1 lower for appendectomy, cholecystectomy, and hysterectomy performed laparoscopically versus open.[32] Inadequate pain control is the most commonly reported negative outcome for ambulatory surgery.[33] The prevalence of chronic postsurgical pain is no different after outpatient than inpatient surgery.[5] Adequate analgesia may be even more challenging for anesthesiologists in ambulatory settings because of the brief period of patient contact.

Ninety-five percent of patients in this investigation had leftover unused opioids. The problem of a growing reservoir of unused opioids and availability for diversion has become increasingly apparent.[34,35] Postoperative opioid prescribing patterns have come under increased scrutiny, and overprescribing has been identified.[36,37] The issue of unused opioids leftover after surgery was recently reviewed, with 77%–92% of outpatients and 67%–90% of inpatients reporting unused

opioids.[38] After upper extremity surgery, patients were prescribed 30 pills, but 77% of patients took ≤15, 45% took <5, and some took none.[39] Our results reinforce the issue of opioid overprescribing in surgical patients, specifically outpatients, and that prescription sizes can be diminished.[1] The second aspect of postoperative opioid prescribing is the novel observation that intraoperative methadone reduced total postdischarge opioid requirements. Thus, intraoperative methadone, by reducing postdischarge opioid consumption, may enable reductions in take-home opioid prescribing and misuse.

There are acknowledged and potential limitations in this investigation. This was a pilot and feasibility study, with small numbers of patients. There was an elevated chance of type I error due to multiple outcomes. Not all patients returned the 30-day diaries. There was a predominance of women, owing to the demographics of the same-day surgery population at the tertiary care academic institution. A fuller comparative investigation, using just 1 methadone dose, and powered for both primary and secondary outcomes, and fuller side-effect analysis, is needed for generalizability. Readiness for PACU discharge was used rather than actual PACU discharge time because the latter is multifactorially determined and nonreflective of actual readiness.[40] To minimize deviations from usual surgical and anesthesia care, PACU analgesia was achieved with short-duration opioids. In our inpatient practice, however, patients receiving intraoperative methadone also receive methadone in the PACU. Such use might confer additional benefit in outpatient anesthesia. Patients and research team members were blinded as to opioid regimen, and PACU opioid dosing was per institutional standard protocol. Anesthesia practitioners were of course not blinded, because, by definition, the study assessed single dosing (methadone) versus conventional multiple intermittent dosing (fentanyl, hydromorphone).

In summary, this investigation found that anesthesia for same-day discharge ambulatory elective surgery using single-dose intraoperative methadone (median dose 9 mg), compared with conventional short-duration opioids, decreased intraoperative and postoperative opioid consumption, and achieved better postoperative analgesia, without increasing side effects.

DISCLOSURES

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Contribution: This author helped revise the manuscript.
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