Original Article

Retrospective cohort study on the effect of intraoperative methadone on postoperative pain and opioid consumption in oral and maxillofacial surgeries

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Background: Opioids are commonly used for pain control after oral and maxillofacial (OMF) surgeries, despite its potential adverse physical and social effects. There has been growing evidence that intraoperative methadone helps reduce postoperative pain and opioid consumption in various surgeries. However, it has not yet been studied in OMF surgeries.

Methods: Following the Partners Human Research Committee approval, a retrospective cohort study identified 185 patients who had OMF surgeries longer than 4 hours between June 30, 2016 to July 1, 2022. Among them, 17 patients were exposed to intraoperative methadone (5–10 mg); 168 patients were identified as the control subjects. The postoperative pain score and opioid consumption in morphine milligram equivalent (MME) in post anesthesia care unit (PACU), 6 hours after surgery and 12 hours after surgery were compared.

Results: The median [interquartile range (IQR)] pain score for methadone group (M group) in PACU, first 6 hours postoperatively and first 12 hours postoperatively were 0.00 (0.00, 5.50), 2.00 (0.00, 4.50), 2.00 (1.50, 4.50); and those for routine group (R group) were 5.00 (2.00, 7.00), 5.00 (3.00, 6.50), 5.00 (3.00, 6.12) respectively. There were statistically significant differences between the pain scores of M group and R group at all three time points (P=0.045, 0.024 and 0.024). After multivariable analysis, the differences remained statistically significant. The total MME (IQR) for M group in PACU, first 6 hours postoperatively and first 12 hours postoperatively were 4.51 (2.52, 7.70), 4.36 (3.35, 9.86), 6.75 (4.50, 9.86); those for R group were 5.03 (3.02, 10.03), 5.60 (3.76, 10.48), 8.85 (4.75, 14.00). There was no statistically significant difference between the two groups at any of the three time points (P=0.527, 0.557, 0.396). No adverse reactions related to opioids were reported in the M group. Time to discharge from PACU was comparable between the two groups (2.33 and 2.47 hours, P=0.664).

Conclusions: a single dose of intraoperative methadone improves postoperative pain after OMF surgeries but does not reduce postoperative opioid consumption. Future comprehensive large-scale studies are needed to validate the safety and efficacy of methadone use in different surgical populations.

Keywords: Methadone; oral and maxillofacial surgery (OMF surgery); postoperative pain; opioid consumption

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Introduction

Background

Postoperative pain control remains a challenging issue after surgery (1), including oral and maxillofacial (OMF) surgeries (2). Opioid medications continue to be the clinical mainstay for postoperative moderate to severe pain (3), and are frequently used after OMF surgeries (2). As proposed by many enhanced recovery after anesthesia protocols, postoperative opioid use is associated with adverse side effects and often delays discharge (4). For many opioid naïve patients, surgery presents a high-risk situation for potentially developing opioid use disorder (OUD) (5). A search for better pain control with less opioids has been an imperative task for perioperative physicians.

Rationale and knowledge gap

While the OMF surgical field has mainly addressed pain control through pre-emptive and post-operative analgesia (6), other surgical specialties have recently gained interest in the choice of particular intraoperative opioids, specifically methadone (7). Methadone has the longest elimination half-life among all opioids used in clinical practice, lasting 24–36 hours (8). Similar to morphine or fentanyl, methadone binds to mu-opioid receptors; however being also an N-methyl-D-aspartate (NMDA) receptor antagonist, methadone helps reduce opioid tolerance and hyperalgesia, and has been shown to improve postoperative pain control and reduce opioid consumption (9). The effect of methadone in OMF surgeries had not been studied.

Highlight box

Key findings

- In this single center retrospective cohort study, intraoperative methadone was shown to be associated with reduced patient-reported postoperative pain score in OMF surgeries longer than 4 hours, without apparent adverse effects.

What is known and what is new?

- Intraoperative intravenous methadone has been shown to be an effective and safe modality to help with postoperative pain and to reduce postoperative opioid consumption in many different surgeries, particularly spine surgeries.
- This study adds to the evidence of methadone use in OMF surgeries being a safe and effective pain modality.

What is the implication, and what should change now?

- Intraoperative methadone can be considered for OMF surgeries for safe and better postoperative pain control. Larger, prospective randomized trials are warranted to further study the use of intraoperative methadone in OMF surgeries, as well as other surgeries that requires opioids for postoperative pain control.

Objective

Here we present a retrospective cohort study in a single quaternary center to examine the effect of a single dose of intraoperative methadone on postoperative pain control and opioid consumption in OMF surgeries. The primary outcome is the median pain score in the post anesthesia care unit (PACU), 6 h after surgery and 12 h after surgery. Secondary outcomes include total opioid consumption in morphine milligram equivalents (MMEs), in PACU, 6 h after surgery and 12 h after surgery, and time to discharge from PACU. We present this article in accordance with the STROBE reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-22-26/rc).

Methods

This study was reviewed by Partners Human Research Institutional Review Board (protocol number: 2019P000449). The IRB has determined that this project meets the criteria for exemption 45 CFR 46.101(b)(#) and no informed consent was required. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

The protocol was approved by Partners Human Research Committee. From the electronic medical record (EMR) system, adults aged 18 and above who underwent OMF surgery, including temporomandibular joint (TMJ) arthroscopy, reconstruction, arthroplasty, and manipulation under general anesthesia at Massachusetts General Hospital from June 30, 2016 to July 1, 2022 were identified. We included surgeries lasting longer than 4 hours (defined by patient's physical presence in operating room longer than 4 hours), as patients undergoing shorter procedures rarely receive methadone in our practice. For patients with multiple qualifying OMF surgeries, only the first time surgery was accounted for in our study. Patients with preexisting substance use disorder including opioid used disorder were excluded. Demographic data including age, gender, race, height, weight, body mass index, American Society of Anesthesiologists (ASA) physical status classification and opioid use history (defined by any exposure to opioid medication in the last 6 months)

were collected. Patients with intraoperative methadone administration was then identified from the anesthesia records first by automatic computer program, then confirmed by 2 independent study member, and assigned to methadone group (M group), while the rest was assigned as routine group (R group). Decision to administer methadone intraoperatively was based solely on attending anesthesiologists' individual practice pattern and evaluation of the patient for risk factors and contraindication. Among patients in the M group, a single intravenous bolus of 5–10 mg methadone was given after induction of anesthesia. All other pain medications, including intravenous ketorolac, intravenous and oral hydromorphone, oral oxycodone, intravenous and oral acetaminophen, patient-controlled hydromorphone pumps were given at the discretion of the attending anesthesiologist while in the operating room, and postoperatively by nurses in the PACU and inpatient floor based on surgeon's orders as needed. Per hospital standard protocol, patient's pain score was recorded using the numeric rating scale of 0–10, where 0 is no pain and 10 is worst pain imaginable, every 1 hour for 3 hours postoperatively in the PACU, and then 1–3 times daily by nursing staff in the ward. All available documented pain scores within the first 12 hours after surgery was collected, and median pain score in PACU, first 6 hours postoperatively and first 12 hours postoperatively were calculated. All available documented opioid medication administration within 12 hours after surgery was collected from the EMR, and total MME consumption in PACU, first 6 hours postoperatively and first 12 hours postoperatively was calculated based on this. We did not extend our data collection to beyond 12 hours postoperatively as most patients are discharged before 12 hours in our practice. For patients in the M group, we manually went through all documentations in EMR 7 days postoperatively for adverse events, including respiratory depression, hemodynamic instability, altered mental status, nausea and vomiting unresponsive to routine as needed antiemetics.

Samples with missing data were dropped from the statistical analysis. Descriptive statistics were reported using mean and standard deviations or medians and 25th and 75 percentiles for continuous variables depending on the data distribution. Categorical variables were summarized using frequencies and percentages. Standardized mean difference (SMD) were reported while a SMD >0.15 was considered as statistically significant difference.

For univariate analysis, we performed a two-independent sample bootstrapped *t*-test to compare the mean differences (MDs) of total MME between the exposure and control groups due to our small study sample size and non-normal data distributions. Bootstrapped 95% confidence intervals were reported. We also performed the traditional *t*-test for result comparisons as sensitivity analysis. For multivariable analyses, we performed multiple linear regression by adjusting for confounding factors of age, sex, race, ASA, and opioid history. Corresponding effect sizes (mean outcome changes between study groups or per unit change of variables) were reported along with their corresponding 95% confidence intervals. Alpha was set to 0.05, and all analyses were performed using R Studio statistical software (Ver. 2022, Boston, MA, USA).

Results

We identified 185 patients who had in total 212 OMF surgeries longer than 4 hours (*Figure 1*). Of them, none were found to have preexisting substance use disorder. For patients with more than one qualifying surgeries, only the first one was included. Intraoperative intravenous methadone dosing was found in 17 patients, who were subsequently enrolled in the M group, while the rest (n=168) were enrolled in the R group. Pain scores of all 185 patients during their first 12 hours after surgery were collected. Four patients in the R group had no pain score documented and was thus excluded from primary outcome analysis. Patient demographics are shown in *Table 1*. The median [interquartile range (IQR)] pain score for M group in PACU, first 6 hours postoperatively and first 12 hours postoperatively were 0.00 (0.00, 5.50), 2.00 (0.00, 4.50), 2.00 (1.50, 4.50); and those for R group were 5.00 (2.00, 7.00), 5.00 (3.00, 6.50), 5.00 (3.00, 6.12) as shown in *Table 2*. There were statistically significant differences between the pain scores of M group and R group at all three time points (P=0.045, 0.024 and 0.024 respectively). After multivariable analysis, the differences remained statistically significant.

Opioid medication administration records of all 185 patients were collected. The total MME (IQR) for M group in PACU, first 6 hours postoperatively and first 12 hours postoperatively were 4.51 (2.52, 7.70), 4.36 (3.35, 9.86), 6.75 (4.50, 9.86); those for R group were 5.03 (3.02, 10.03), 5.60 (3.76, 10.48), 8.85 (4.75, 14.00), as shown in *Table 3*. There was no statistically significant difference between the two groups at any of the three time points (P=0.527, 0.557, 0.396).

The median time to discharge from PACU was 2.33 hours in M group and 2.47 hours in R group. There

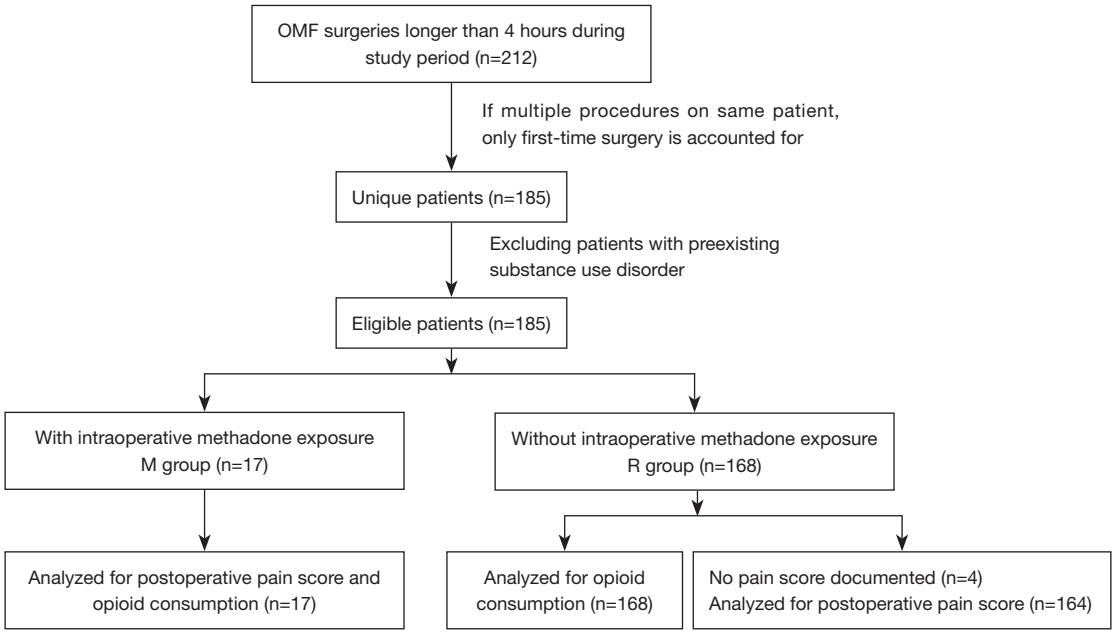

Figure 1 Patient enrollment and allocation to methadone and routine groups. OMF, oral and maxillofacial; M, methadone; R, routine.

was no statistically significant difference between the time to discharge from PACU between the two groups (P=0.664). For the 17 patients in the M group, no documentation of adverse events, including respiratory depression, hemodynamic instability, altered mental status, nausea and vomiting unresponsive to routine as needed antiemetics were found in the EMR within 7 days postoperatively.

Discussion

Key findings

Our study showed that intraoperative methadone use is associated with lower pain score in the first 12 hours postoperatively, but no difference in postoperative opioid consumption.

Strengths and limitations

Our study is the first we know of that focuses on the use of intraoperative methadone in OMF surgeries and adds to the evidence that methadone is a safe and effective modality for postoperative pain control. Our study has some limitations. First, the sample size is small, especially for the methadone group, as intraoperative methadone dosing is not yet widely accepted by our clinicians. We are actively working on expanding our study period to find more eligible patients. Also, many patients were discharged on day of surgery or postoperatively day 1, making it impossible for us to collect pain and opioid use data beyond 24 h retrospectively, a prospectively designed study where we actively collect these data will solve this issue. Finally, as we rely on existing documentations in the EMR, some mild-to-moderate opioid related side effects that had not been documented in EMR might have been missed in our study.

Comparison with similar researches

Previous meta-analysis by Machado *et al.* (7) concluded that intraoperative use of methadone reduced postoperative pain compared to other opioids and also reduced postoperative opioid consumption. This meta-analysis included studies on cardiac, spine, abdominal, gynecological, orthopedic, urologic, and bariatric procedures. Recent accumulation of evidence for intraoperative methadone use, especially with high-quality randomized controlled trials in spine surgeries (10), where postoperative pain control is often a challenge, have encouraged anesthesia providers to include methadone back in their pain control arsenal. We have seen an increase in intraoperative methadone dosing in spine surgeries at our institution. However, this has not yet to expand to other surgeries. Our study suggested new

Table 1 Demographic characteristics for all participants (N=185)

Characteristics	Methadone group (n=17)	Routine group (n=168)	SMD
Age, years, mean ± SD	38.0±14.1	44.5±17.1	0.412
Gender, n (%)			0.021
Female	13 (76.5)	127 (75.6)	
Male	4 (23.5)	41 (24.4)	
Race, n (%)			0.524
Asian	0 (0.0)	7 (4.2)	
Black	0 (0.0)	10 (6.0)	
White	16 (94.1)	137 (81.5)	
Other	1 (5.9)	11 (6.5)	
NA	0 (0.0)	3 (1.8)	
Weight, kg, mean ± SD	61.2±12.7	72.5±19.7	0.687
BMI, kg/m^2, mean ± SD	22.6±5.0	26.0±6.1	0.603
ASA, n (%)			0.483
1	3 (20.0)	20 (13.2)	
2	7 (46.7)	97 (63.8)	
3	4 (26.7)	35 (23.0)	
4	1 (6.7)	0 (0.0)	
Height, cm, mean ± SD	164.7±9.9	166.6±9.2	0.203
Opioid history, n (%)			0.444
No	4 (23.5)	74 (44.0)	
Yes	13 (76.5)	94 (56.0)	

There are significantly more patients with opioid use history in the methadone group. Race other than White, Black and Asian were reported as "Other"; if not available in the chart, is reported as "NA". SD, standard deviation; SMD, standardized mean difference; BMI, body mass index; ASA, American Society of Anesthesiologists physical status classification.

Table 2 Postoperative pain score

Variables	Methadone group (n=17)	Routine group (n=164)	P value
In PACU, median (IQR)	0.00 (0.00, 5.50)	5.00 (2.00, 7.00)	0.045*
6 h postop, median (IQR)	2.00 (0.00, 4.50)	5.00 (3.00, 6.50)	0.024*
12 h postop, median (IQR)	2.00 (1.50, 4.50)	5.00 (3.00, 6.12)	0.024*

Methadone group had significantly lower pain score at all three time points compared to routine group. *, statistical significance. PACU, post anesthesia care unit; IQR, interquartile range.

Table 3 Perioperative opioid consumption in MME

Variables	Methadone group (n=17)	Routine group (n=168)	P value
Intraop, total (IQR)	13.68 (10.00, 20.01)	20.00 (15.00, 29.40)	0.027
In PACU, total (IQR)	4.51 (2.52, 7.70)	5.03 (3.02, 10.03)	0.527
6 h postop, total (IQR)	4.36 (3.35, 9.86)	5.60 (3.76, 10.48)	0.557
12 h postop, total (IQR)	6.75 (4.50, 9.86)	8.85 (4.75, 14.00)	0.396

Methadone group had significantly less intraoperative opioid exposure. No statistically significant differences in the amount of opioids consumed at all three time points postoperatively. MME, morphine milligram equivalent; PACU, post anesthesia care unit; IQR, interquartile range.

evidence supporting benefits of methadone use specifically in OMF procedures.

Most studies on intraoperative methadone focus on pain benefit 24, 48 and 72 hours after surgery (10-12), we evaluated pain score and opioid consumption within the first 12 hours after surgery, as the majority of our patients get discharged on day of surgery or the following day. We have shown benefits of methadone on patient reported pain score in the immediately postoperative timeframe up to 12 hours postoperatively. This is consistent with previous study in cardiac patients which also showed less pain with coughing with methadone in the first 12 hours postoperatively (13). It should be noted that in our study this immediate pain benefit is in the setting of actually receiving less opioids intraoperatively.

Explanations of findings

The pain benefit of intraoperative methadone is likely a result from methadone creating a more stable circulating opioid level, causing less fluctuation during the titration of shorter-acting opioids. Our study did not demonstrate a statistically significant effect on reducing postoperative opioid consumption, however there is a trend towards less opioids in the M group. Despite a relatively small sample size, there were no reported adverse effects in the methadone, demonstrating again that a single dose of 0.1–0.2 mg/kg of intravenous methadone is a safe option for postoperative pain control.

Implications and actions needed

Two obstacles for more expanded use of intraoperative intravenous methadone are its unpredictable pharmacokinetics, and unique side effects. Being metabolized by the cytochrome P450 enzymes (14), methadone has high interpersonal metabolic variability and multiple drug-drug interaction that requires more considerations compared to other opioids. QTc prolongation effect of methadone makes close drug monitoring in long-term dosing necessary (15), but the side effects of a single low-dose administration remain to be investigated. Similar to previous report (10), our study demonstrated no difference in the time to discharge from PACU between the two groups. We also did not identify any methadone-related adverse reactions in the 17 patients in M group, which is consistent with previous reports (12). These evidence makes us wonder the value of intraoperative methadone dosing in ambulatory surgeries since better and more stable pain control is especially valuable in this setting as pain is an obstacle to discharge and more difficult to manage for patients going home. In the pilot study in the ambulatory surgery by Komen *et al.* (16), median dose of 6 and 9 mg of intraoperative methadone were both trialed in same-day surgery patients, with no increased opioid-related adverse reactions. Further large-scale clinical studies are needed to verify the safety of methadone.

Conclusions

In this retrospective cohort study, a single dose of intraoperative methadone improves patient reported pain score after OMF surgeries, but does not reduce postoperative opioid consumption. More comprehensive large-scale studies are needed to validate the safety and efficacy of methadone use in different surgical populations.

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Footnote

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