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Intraoperative intravenous methadone dose and postoperative pain outcomes in CABG patients: a retrospective cohort study

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Abstract

Background

Evidence supports intraoperative methadone for reducing opioid use and improving pain management in cardiac surgery. However, the optimal dose for patients undergoing coronary artery bypass grafting (CABG) remains unclear. We conducted a retrospective cohort study comparing low-dose (< 20 mg) versus high-dose (≥ 20 mg) intravenous methadone to evaluate postoperative pain management and opioid requirements during the first 72 hours after surgery.

Methods

A retrospective chart review was conducted of patients who underwent CABG between January 1, 2021, and September 30, 2024. Patients were separated into low-dose and high-dose groups based on the intraoperative methadone dose received. Opioid requirements were assessed during the 72 hours postoperatively, expressed as oral morphine milligram equivalents (MME). Additionally, postoperative pain scores (utilizing the numeric rating scale [NRS]), total days spent in the intensive care unit (ICU), time to extubation, QTc interval exceeding 500 ms at any point during the 72 hours postoperatively, and naloxone use were also evaluated.

Results

A total of 41 patients were evaluated (20 patients in the low-dose cohort and 21 patients in the high-dose cohort). The total 72-hour postoperative opioid consumption did not differ significantly between patients who received low-dose versus high-dose intraoperative IV methadone (86.1 ± 75.7 vs 150.1 ± 153.6 MME; p = 0.098). No statistically significant differences were observed in postoperative pain scores, ICU length of stay, time to extubation, or QTc prolongation (> 500 ms).

Conclusions

There were no statistically significant differences in postoperative opioid consumption during the first 72 hours between CABG patients who received low-dose versus high-dose intraoperative intravenous methadone. Additionally, no statistically significant differences were observed in postoperative pain scores, ICU length of stay, time to extubation, or QTc prolongation (> 500 ms).

INTRODUCTION

Coronary artery bypass grafting (CABG) is the most common type of major cardiac surgery performed in the United States, and postoperative pain management is essential for optimizing recovery. Patients undergoing cardiac surgery frequently experience significant postoperative pain due to factors such as

surgical incisions, sternotomy, rib retraction or fracture, and chest tube placement, with severity peaking on postoperative (POD) days 0 and 1.[1–3,7] Pain can trigger physiologic responses that may lead to postoperative complications and an increased risk of chronic pain.[4] Acute complications of inadequate pain control include respiratory complications (e.g., pneumonia, respiratory depression), cardiovascular events (e.g., myocardial ischemia, arrhythmias), and prolonged mechanical ventilation. Long-term complications include chronic pain syndrome and overall delayed recovery.[4,5] Although opioids are frequently used agents for postoperative pain control, increased opioid exposure can result in respiratory depression, ileus, and other adverse effects.[3–6]

The analgesic properties of methadone are primarily through μ-opioid receptor agonism, with additional effects achieved by N-methyl-D-aspartate (NMDA) receptor antagonism.[5,9] While methadone has traditionally been used for the management of chronic pain or opioid use disorder, its long half-life and analgesic properties have led to its consideration for intraoperative pain control. Perioperative pain management often relies on the recurrent administration of short-acting opioids such as fentanyl or hydromorphone. However, this approach may result in fluctuating serum concentrations that can lead to suboptimal analgesia, brief periods of adequate pain control, or toxicity. [8–10] In contrast, methadone's long half-life contributes to extended analgesic effects, with data suggesting that an intravenous bolus dose of 20–30 mg may offer pain relief for approximately 24–36 hours.[2,8] However, methadone use has been associated with respiratory depression, QT prolongation, variable pharmacokinetics, and longer postoperative mechanical ventilation, highlighting the need for careful dosing and monitoring.[11]

Clinical trials in opioid-naïve patients have administered methadone at doses ranging from 0.1–0.3 mg/kg for perioperative analgesia, with many studies favoring 0.2 mg/kg or a fixed-dose regimen.[8,9] Previous studies have also used a fixed dose of 20 mg, which provides a more favorable pharmacokinetic profile and sustained analgesia compared with lower doses.[8,13] This is supported by prior pharmacokinetic–pharmacodynamic data that showed doses of approximately ≥ 20 mg allow for longer time above the minimum effective concentration (MEC), resulting in the duration of analgesia aligning with the drug's elimination half-life.[8] At UC San Diego Health, institutional guidance recommends either 0.2 mg/kg or fixed intravenous doses (e.g., 10 mg, 15 mg, or 20 mg) at anesthesia induction for perioperative methadone administration. The guidance also notes that doses may need to be adjusted based on patient characteristics, such as opioid tolerance and age.[14]

Although existing studies support the efficacy of perioperative methadone, the optimal dose in CABG patients remains uncertain. Therefore, the objective of this study was to compare postoperative opioid consumption between CABG patients receiving low-dose versus high-dose intraoperative intravenous methadone. We hypothesized that intraoperative methadone dose (low-dose vs high-dose) would be associated with differences in opioid consumption during the first 72 hours after surgery.

METHODS

Study Design and Data Collection

The study was conducted via retrospective chart review at a single academic medical center. It was approved by the institutional review board, and informed consent was not required. Adults who underwent CABG and received perioperative methadone between January 1, 2021, and September 30, 2024, were included in the study. Patients were excluded if they were intubated for longer than 12 hours, had a history of illicit drug use, or underwent a subsequent operation within 72 hours of the CABG. Patients were also excluded if they did not have any QTc interval data or were extubated in the operating room.

Patients were grouped into low-dose (< 20 mg) and high-dose (≥ 20 mg) groups based on the intraoperative methadone dose received. The intraoperative methadone dose was primarily driven by provider preference and institutional guidance. Baseline characteristics that were collected include gender, age, weight, height, prior chronic opioid use, and intraoperative methadone doses.

Outcome Measures

The study's primary outcome was total opioid consumption during the first 72 postoperative hours, expressed as oral morphine milligram equivalents (MME) using previously established opioid conversions. MME totals were calculated separately for each postoperative day and cumulatively over the first 72 postoperative hours (sum of PODs 1–3). POD 1 was defined as the day after surgery, beginning at midnight, with POD 2 and POD 3 defined similarly. The following secondary outcomes were compared between the two groups: postoperative pain scores on PODs 1–3, total days spent in the intensive care unit (ICU), time to extubation, QTc > 500 ms at any point during the 72 postoperative hours, and naloxone use. Mean pain scores were calculated for each postoperative day, excluding any scores recorded within 2 hours of opioid administration to avoid possible masking of pain symptoms due to the previously administered opioid.

Statistical Analysis

Continuous variables were summarized as means ± standard deviations or median (interquartile range). Comparisons for baseline characteristics were performed using the Mann-Whitney U test or independent samples t-test based on distribution, and Fisher's exact test or chi-square test for categorical variables. Primary outcome comparisons were performed using two-sample Student's t-tests and chi-squared tests. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Among the 124 patients initially screened, 62 met the inclusion criteria. Twenty-one patients were subsequently excluded due to incomplete records or other predefined exclusion criteria. Exclusions included missing QTc data (n = 6), extubation in the operating room (n = 4), intubation > 12 hours (n = 3),

history of illicit drug use (n = 5), and a subsequent operation within 72 hours of CABG (n = 1). Two patients met multiple exclusion criteria, including being intubated for longer than 12 hours and undergoing a subsequent operation within 72 hours. A total of 41 patients were included in the final analysis (low-dose cohort: n = 20; high-dose cohort: n = 21). Baseline characteristics are presented in Table 1. All patients were opioid naive, and no patients required naloxone during their admission. The high-dose had significantly higher weight, BMI, and methadone doses (mg/kg).

Table 1
Baseline Characteristics

Age (years), median (IQR)	**Low-Dose (< 20 mg)**	**High-Dose (≥ 20 mg)**	**P Value**
	(n = 20)	**(n = 21)**	
	66 (60–69)	**66 (57–70)**	**0.804**
Male sex, no. (%)	16 (80%)	18 (86%)	0.697
Weight (kg), median (IQR)	74.2 (65.4–85.2)	95.6 (87.5–105.8)	< 0.001
BMI (kg/m^2), mean (SD)	28 (4)	33 (5)	0.001
Prior chronic opioid use, no. (%)	0 (0%)	0 (0%)	-----
Methadone Doses (mg/kg), median (IQR)	0.17 (0.13–0.19)	0.23 (0.19–0.25)	< 0.001
Type of Cardiac Surgery, no. (%)			
CABG Alone	13 (65%)	14 (67%)	
CABG + Endarterectomy	4 (20%)	2 (9.5%)	
CABG + Aortic Valve/Mechanical Valve Replacement	2 (10%)	1 (4.5%)	
CABG + Aortic Arch Replacement	0 (0%)	2 (9.5%)	
CABG + Sternotomy	1 (5%)	2 (9.5%)	
Intraoperative Methadone Doses, no. (%)			
5 mg	1 (5%)		
10 mg	9 (45%)		
15 mg	10 (50%)		
20 mg		16 (76%)	
25 mg		3 (14.5%)	
30 mg		2 (9.5%)	

Postoperative opioid consumption and pain scores for the two groups are presented in Table 2. The total opioid consumption during the first 72 postoperative hours did not differ significantly between groups (86.1 ± 75.7 MME vs 150.1 ± 153.6 MME; p = 0.098).

Table 2
Postoperative Opioid Requirements and Pain Scores

	Low-Dose (< 20 mg) (n = 20)	**High-Dose (≥ 20 mg) (n = 21)**	**P Value**
Postoperative Opioid Requirements, mean (SD), MME			
POD 1	42.3 (40.0)	64.2 (55.5)	0.155
POD 2	25.8 (25.0)	51.2 (63.7)	0.102
POD 3	17.9 (21.3)	34.8 (41.2)	0.108
72 Hour Total	86.1 (75.5)	150.1 (153.6)	0.098
Postoperative Pain Scores, mean (SD)			
POD 1	3.3 (2.2)	3.9 (1.9)	0.374
POD 2	2.8 (1.9)	3.9 (2.5)	0.113
POD 3	2.3 (2.6)	2.8 (1.9)	0.452
Abbreviations: SD, standard deviation; MME, morphine milligram equivalent; POD, postoperative day			

On POD 1, patients in the low-dose group had numerically less opioid consumption than those in the high-dose group (42.3 ± 40.0 vs 64.2 ± 55.5 MME; p = 0.155). Opioid consumption in the low-dose group continued to be lower on POD 2 (25.8 ± 25.0 MME vs 51.2 ± 63.7 MME; p = 0.102) and POD 3 (17.9 ± 21.3 MME vs 34.8 ± 41.2 MME; p = 0.108), although these differences were not statistically significant. Across both cohorts, opioid consumption was highest on POD 1 and declined over subsequent postoperative days. These trends, along with postoperative pain scores, are further illustrated in Fig. 1.

Additionally, no statistically significant differences in postoperative pain scores were observed between the two cohorts. Mean pain scores were numerically lower in the low-dose group compared with the high-dose group on POD 1 (3.3 vs 3.9; P = 0.374), POD 2 (2.8 vs 3.9; P = 0.113), and POD 3 (2.3 vs 2.8; P = 0.452). In the high-dose group, mean pain scores were the same on POD 1 and POD 2, with scores in both cohorts declining over the postoperative course.

Results for the secondary endpoints are shown in Table 3. There were no statistically significant differences observed in ICU length of stay, time to extubation, or QTc prolongation between the two groups. The median ICU length of stay was 2.0 days (IQR, 1.8–2.0) in the low-dose group compared with 2.0 days (IQR, 1.0–3.0) in the high-dose group (p = 0.386). Median time to extubation between the two groups was 4.0 hours (IQR, 3.8–5.0) and 5.0 hours (IQR, 4.0–6.0) respectively (p = 0.129). QTc

prolongation occurred in 2 patients (10%) in the low-dose group and 5 patients (24%) in the high-dose group (p = 0.24).

Table 3
Secondary Endpoints

ICU Length of Stay (days), median (IQR)	**Low-Dose (< 20 mg) (n = 20)**	**High-Dose (≥ 20 mg) (n = 21)**	**P Value**
	2.0 (1.8–2.0)	**2.0 (1.0–3.0)**	**0.386**
Time to Extubation (hrs), median (IQR)	4.0 (3.8–5.0)	5.0 (4.0–6.0)	0.129
QTc > 500 ms, no. (%)	2 (10%)	5 (24%)	0.240
Naloxone Use, no. (%)	0 (0%)	0 (0%)	-----

DISCUSSION

In this retrospective cohort study, intraoperative intravenous methadone dose was not associated with differences in postoperative opioid consumption during the first 72 hours after surgery. To our knowledge, this is the first study to evaluate the impact of two different intraoperative methadone dosing strategies on postoperative pain control and opioid requirements in CABG patients. Patients in the high-dose group had numerically higher opioid consumption on each postoperative day and across the overall postoperative period. Although no differences in pain scores were observed between groups, pain scores were numerically lower in the low-dose group across all postoperative days. Mean pain scores remained low in both groups, suggesting that pain was well controlled throughout the postoperative period. Together, these findings suggest that lower intraoperative methadone dosing may provide comparable analgesia to higher dosing strategies within the ranges evaluated.

ICU length of stay and time to extubation were similar between groups, with no statistically significant differences observed. QTc prolongation occurred more frequently in the high-dose group compared with the low-dose group (24% vs 10%). Of note, the low-dose group had comparable pain control with a lower risk of prolongation. Although this difference was not statistically significant, this suggests that closer QTc monitoring may be warranted in patients who receive intraoperative methadone, especially at higher doses.

Limited evidence exists evaluating the association between a single intraoperative methadone dose and QTc prolongation. A retrospective cohort study of patients undergoing major non-cardiopulmonary surgery compared intraoperative methadone (0.1–0.2 mg/kg, maximum 20 mg) with non-methadone regimens and found no significant difference in QTc prolongation (> 500 ms) between groups (23.8% vs 23.0%; p = 0.88).[15] A second retrospective cohort study in cardiac surgery patients compared those who received a single perioperative intravenous methadone dose (0.1 mg/kg) with those who received non-methadone analgesic regimens and similarly demonstrated no significant differences in immediate

postoperative QTc interval (473.2 ± 56.1 vs 472.5 ± 57.2; p = 0.86) or percent change in QTc (0.1 ± 0.1 vs 0.1 ± 0.1; p = 0.32).[16] However, in contrast to studies comparing methadone with non-methadone cohorts, our analysis evaluated QTc prolongation across different methadone dosing strategies, addressing a current gap in the literature. It is important to note that we did not account for concomitant use of other QTc-prolonging medications, which limits the interpretation of these findings.

These safety findings should be interpreted in the context of established evidence supporting the analgesic efficacy of intraoperative methadone. In a randomized, double-blind trial, patients undergoing elective cardiac surgery with cardiopulmonary bypass were evaluated.[17] Patients who received methadone (0.3 mg/kg) had significantly lower 24-hour postoperative morphine consumption (median 6 mg vs 10 mg, P < 0.001) and pain scores with coughing at 12 hours (median score 4 vs 6, P < 0.001) compared with fentanyl (12 μg/kg). Similarly, a randomized trial evaluated methadone (0.2 mg/kg) versus morphine (0.2 mg/kg) in patients undergoing elective cardiac surgery via sternotomy, including CABG and valve procedures.[12] Methadone significantly reduced 24-hour opioid requirements (median 9 mg vs 24 mg, P < 0.001) and was associated with lower postoperative pain scores at rest (β -2.24, standard error 0.49, p < 0.001) and while coughing (β -2.16, standard error 0.50, p < 0.001). There was no significant difference in opioid-related adverse events between the two groups. In contrast to these randomized trials, which compared methadone with alternative opioid regimens, our study evaluated low-dose versus high-dose intraoperative methadone dosing strategies and found no significant differences in postoperative opioid consumption, pain scores, or key safety endpoints.

This study has several limitations. The relatively small sample size from a single academic medical center may limit the generalizability of the findings. Pain score assessment was another limitation, as pain score calculations excluded values recorded within 2 hours of opioid administration to minimize potential masking of pain due to prior opioid dosing. In addition, pain scores were documented at varying frequencies by different nursing staff, which may result in inconsistent measurement of pain scores. Other multimodal analgesic strategies and nonpharmacologic interventions were not assessed and may have influenced patient outcomes. Lastly, institutional guidance at UC San Diego Health allows for intraoperative methadone dosing using either weight-based (0.2 mg/kg) or fixed dosing strategies (e.g., 10, 15, or 20 mg), and provider discretion in selecting dosing approaches may have introduced confounding not fully captured in the analysis. Notably, patients in the high-dose methadone group had significantly higher body weight and body mass index compared to those in the low-dose group, which may have important clinical implications. It is possible that the lack of observed differences in opioid requirements and pain scores reflects appropriate dose selection for patient body habitus rather than true equivalence between dosing strategies. Given that dosing was not controlled for weight in this analysis, it remains unclear whether lower methadone doses would yield comparable outcomes in patients with higher body weight, as this was not directly evaluated in the present study.

Future studies are needed to further assess the optimal intraoperative methadone dosing strategy in cardiac surgery patients. Larger, randomized trials may better characterize patient-specific factors, such as age, comorbidities, and anticipated pain burden, to inform individualized dosing approaches.

Additionally, comparisons between fixed-dose and weight-based strategies may further clarify the most appropriate approach to intraoperative methadone dosing. We observed that a relatively small proportion of intraoperative intravenous methadone use at our institution occurred in CABG patients. This highlights the need for future studies to evaluate methadone dosing strategies and associated outcomes in other surgical cohorts to enhance generalizability and inform perioperative analgesic practice.

CONCLUSION

There were no statistically significant differences in postoperative opioid consumption during the first 72 hours between CABG patients who received low-dose versus high-dose intraoperative IV methadone. Additionally, there were no statistically significant differences observed in postoperative pain scores, ICU length of stay, time to extubation, or QTc prolongation (> 500 ms). These findings suggest that lower doses of methadone may provide comparable analgesia within the dosing ranges evaluated, although larger prospective studies are needed to confirm these results.

Abbreviations

BMI
body mass index
CABG
coronary artery bypass grafting
ICU
intensive care unit
NMDA
N-methyl-D-aspartate
NRS
numeric rating scale
MEC
minimum effective concentration
MME
morphine milligram equivalents
POD
postoperative day

Declarations

Ethics approval and consent to participate:

This study was approved by the Institutional Review Board of the University of California, San Diego (UC San Diego Office of IRB Administration) on August 6, 2025 (IRB No: 811400). All aspects of this study were conducted in accordance with the Declaration of Helsinki and relevant institutional regulations. As

this was a retrospective cohort study, informed consent to participate was waived by the UC San Diego Institutional Review Board (IRB No: 811400).

Consent for publication:

Not applicable

Competing interests

The authors declare that they have no competing interests.

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None

Author Contribution

Data collection and analysis: MA. Writing-original draft: MA. Writing-review and editing: WH and AT. All authors read and approved the final manuscript.

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Data Availability

Data will be available from the corresponding author upon reasonable request and is subject to institutional approval where applicable.

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Figures

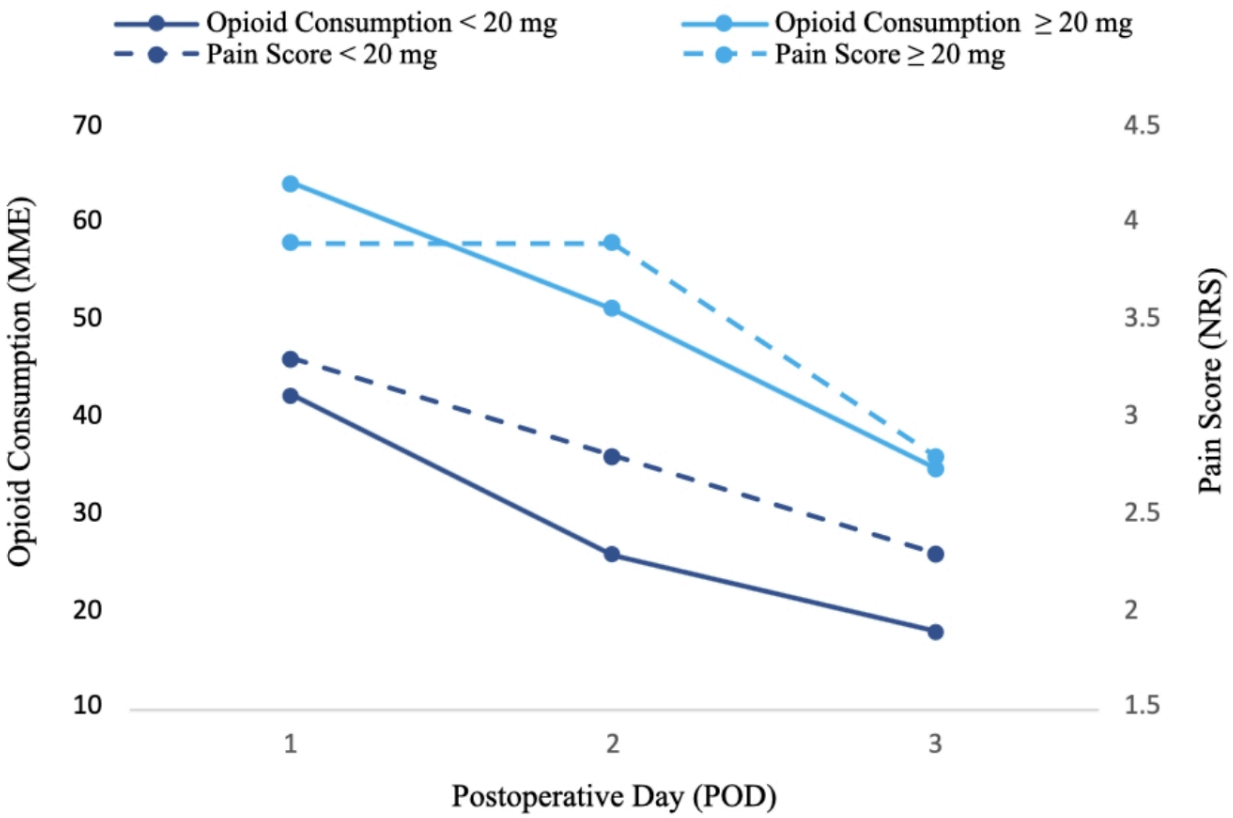


Figure 1

Line graph of postoperative opioid consumption (MME) and pain scores (NRS) over POD 1–3 by methadone dose group.