BJA Open

BJA Open, 10 (C): 100270 (2024)

doi: 10.1016/j.bjao.2024.100270
Original Research Article

ORIGINAL RESEARCH ARTICLE

The role of methadone in cardiac surgery for management of postoperative pain

Jordan N. Edwards[1], Madeline A. Whitney[2], Bradford B. Smith[3], Megan K. Fah[3], Skye A. Buckner Petty[4], Omar Durra[5], Kristen A. Sell-Dottin[6], Erica Portner[7], Erica D. Wittwer[7] and Adam J. Milam[3,4,*]

[1]Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA, [2]Mayo Clinic Alix School of Medicine, Scottsdale, AZ, USA, [3]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Phoenix, AZ, USA, [4]Department of Quantitative Health Sciences, Mayo Clinic, Phoenix, AZ, USA, [5]Keck School of Medicine of USC, Los Angeles, CA, USA, [6]Department of Cardiovascular Surgery, Mayo Clinic, Phoenix, AZ, USA and [7]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA

*Corresponding author. Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Phoenix, AZ, USA. E-mail: milam.adam@mayo.edu

Abstract

Background: This retrospective study evaluated the efficacy and safety of intraoperative methadone compared with short-acting opioids.
Methods: Patients undergoing cardiac surgery with cardiopulmonary bypass (n=11 967) from 2018 to 2023 from a single health system were categorised into groups based on intraoperative opioid administration: no methadone (Group O), methadone plus other opioids (Group M+O), and methadone only (Group M).
Results: Patients in Groups M and M+O had lower mean pain scores until postoperative day (POD) 7 compared with Group O after adjusting for covariates (P<0.01). Both Groups M and M+O had lower total opioid administered compared with Group O for all days POD0–POD6 (all P<0.001). The median number of hours until initial postoperative opioid after surgery was 2.55 (inter-quartile range [IQR]=1.07–5.12), 6.82 (IQR=3.52–12.98), and 7.0 (IQR=3.82–12.95) for Group O, Group M+O, and Group M, respectively. The incidence of postoperative complications did not differ between groups.
Conclusions: Intraoperative administration of methadone was associated with better pain control without significant side-effects after cardiac surgery.

Keywords: acute pain; cardiac surgery; methadone; opioids; postoperative complications

Short-acting opioids (e.g. hydromorphone, fentanyl) have been used to induce and maintain analgesia during balanced anaesthesia for cardiac procedures requiring sternotomy because they are associated with cardiovascular stability.[1,2] Despite high-dose opioid administration, >75% of cardiac surgery patients report moderate to severe pain 1 week after surgery,[3] leading to adverse outcomes such as pulmonary dysfunction, arrhythmias, and myocardial ischaemia.[4] In addition, repeated use of short-acting opioids is associated with numerous side-effects, including tolerance, physical dependence, immunosuppression, constipation, postoperative nausea and vomiting (PONV), urinary retention, opioid-induced hyperalgesia, sedation, corrected QT interval (QTc) prolongation, and respiratory depression.[5,6] Postoperative pain management is critical in achieving patient-centred outcomes and reducing hospital length of stay (LOS).[7]

Methadone is a long-acting μ-opioid agonist and an antagonist at the N-methyl-D-aspartate (NMDA) receptor that has emerged as a potential alternative to improve pain control after cardiac surgery.[8] When administered in larger doses (>20 mg), methadone provides analgesia for 24–36 h.[8] Studies have demonstrated benefits in postoperative pain management

Received: 22 December 2023; **Accepted:** 27 February 2024

after a single dose of intraoperative methadone compared with shorter-acting opioids.[9] Recent evidence supports the effectiveness of methadone in reducing postoperative cardiac surgical pain and opioid consumption without incurring additional adverse effects within the first 24 h after surgery.[10]

The utility of methadone in cardiac surgery demands a more comprehensive investigation. Although initial research appears promising, small sample sizes limit the external validity of the results.[11] Systematic reviews are restricted by the small number of studies focusing on this clinical question.[10] Significant uncertainties and avenues for future investigation that remain are the timing and dosage of methadone administration, examination of adverse outcomes, and long-term efficacy and side-effect profile.[10,12]

This study seeks to address several of those gaps, investigating the effectiveness and safety of intraoperative methadone administration compared with shorter-acting opioids among cardiac surgery patients up until postoperative day (POD) 7.[13,14] We hypothesised that methadone would provide superior pain control compared with shorter-acting opioids and that methadone would not be associated with additional postoperative complications compared with shorter-acting opioids.[15,16] Findings from this study could enhance our understanding of methadone's potential role in postoperative pain management, offering further insights for future clinical practice and guidelines.

Methods

Overview

This is a retrospective cohort of patients 18 yr or older, undergoing cardiac surgery with cardiopulmonary bypass (CPB; Table 1) between the dates of 5 May 2018 and 26 May 2023. The Mayo Clinic institutional review board approved this retrospective study (Mayo Clinic IRB Number 22–007486), and all patients included granted permission to use their medical records for research. Patients who declined research authorisation were excluded. Patients who did not receive an anaesthetic during their procedure, underwent transplantation, or died intraoperatively were also excluded (Fig. 1). All patients went to the intensive care unit (ICU) after their index cardiac procedure. Cases were performed in the main operating room between four hospital campuses from one large health system (Mayo Clinic).

Variables and data collection

The study cohort was identified utilising an institutional, enterprise-wide DataMart within Mayo Clinic. This validated database contains detailed perioperative information related to the patient's surgical encounter and hospital stay. Any information not readily available in the perioperative DataMart was extracted using the Advanced Text Explorer and Mayo Data Explorer, other validated institutional software containing patient-specific clinical data.

Outcomes

The primary outcome of interest was the daily mean pain score from the verbal rating scale (0 to 10; higher scores indicate more pain). The secondary outcomes were the daily total oral morphine equivalents (OME; Supplementary Table S1) and the time until first opioid administration in the ICU. Patients who did not receive postoperative opioids were censored at discharge. We examined daily mean pain score and daily total OME until POD7 or until patients were discharged from the ICU, resulting in varying sample sizes from POD0 to POD7. Exploratory outcomes include opioid-related complications: pruritis, urinary retention, and changes in QTc. Change in QTc interval was only assessed in patients who had QTc interval measurements within 7 days before and 2 days after surgery.

Predictors

Patients were categorised into three groups based on intraoperative administration of methadone: no methadone (Group O), methadone plus other opioids (Group M+O), and methadone only (Group M).

Covariates

The following covariates were included in the regression model based on their relationship with pain scores and opioid administration[19]: age, body mass index (BMI), sex, year of surgery, Charlson Comorbidity Index, smoking status (current, former, or never smoker), history of chronic pain, diagnosis of fibromyalgia, use of home opioid within 90 days of surgery, administration of antiemetics and non-opioid analgesics before surgery, intraoperative administration of antiemetics and non-opioid analgesics, preoperative or intraoperative regional block, use of local anaesthetics by the surgical team, length of surgery (i.e. operating theatre time), and surgery type.

Statistical analysis

Missing values within the covariates were handled by single imputation. No outcome variables were imputed, therefore, the sample sizes for all statistical models were the same as the number observed outcome values. A previous study found an average pain score of 1.9 in the methadone group and 2.6 in the control group.[10] To detect a similar effect with 90% power, estimated by a quantile regression model, 130 subjects were needed. Our sample was much larger allowing for the addition of several covariates. Covariates were summarised using frequencies and percentages for categorical variables (including year of surgery), and median and inter-quartile range (IQR) anchors for numerical variables. For convenience, IQR is used to reference the first and third quartiles instead of the computed range. Differences within covariates by methadone group were assessed with χ^2 tests and Kruskal–Wallis rank sum tests for categorical and numerical variables, respectively. Daily mean pain scores and daily administered OME were also summarised using median and IQR. Differences in these outcomes by methadone group were assessed with quantile (median) regression models adjusting for covariates. Differences in time to tracheal extubation and ICU and hospital LOS were also assessed with quantile regression. Differences in the length of time from end of surgery to first administered opioid were compared using Kaplan–Meier curves and covariate-adjusted cox proportional hazards models. Differences in rates of postoperative pruritis, urinary retention, naloxone usage, and PONV were assessed with covariate-adjusted logistic regression models. Change in QTc interval was compared between groups using covariate-adjusted linear regression. For all regression models, the no methadone group was the reference group. Sensitivity

Table 1 Descriptive characteristics of patients, stratified by methadone administration. ACHD, adult congenital heart disease; BMI, body mass index; CABG, coronary artery bypass graft. *Preoperative non-opioid analgesic: acetaminophen, celecoxib, gabapentin, ketamine, and pregabalin.

	Group O (*n*=4386)	Group M+O (*n*=4859)	Group M (*n*=1997)	Total (*n*=11 242)	*P*-value
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Age (yr)	65.0 (56.0–72.0)	64.0 (54.0–71.0)	64.0 (54.0–71.0)	65.0 (55.0–72.0)	<0.001
BMI (kg m^{-2})	28.1 (24.8–32.2)	28.7 (25.2–33.0)	28.6 (25.1–32.9)	28.4 (25.0–32.7)	<0.001
Male	2961 (67.5)	3288 (67.7)	1324 (66.3)	7573 (67.4)	0.528
Year of surgery					
2018	1306 (29.8)	16 (0.3)	32 (1.6)	1354 (12.0)	<0.001
2019	683 (15.6)	463 (9.5)	1144 (57.3)	2290 (20.4)	
2020	765 (17.4)	949 (19.5)	365 (18.3)	2079 (18.5)	
2021	814 (18.6)	1285 (26.4)	183 (9.2)	2282 (20.3)	
2022	596 (13.6)	1539 (31.7)	230 (11.5)	2365 (21.0)	
2023	222 (5.1)	607 (12.5)	43 (2.2)	872 (7.8)	
Median Charlson Comorbidity Index	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	<0.001
Smoking status					0.080
Current smoker	290 (6.6)	346 (7.1)	105 (5.3)	741 (6.6)	
Former smoker	1617 (36.9)	1799 (37.0)	740 (37.1)	4156 (37.0)	
Never smoker	2479 (56.5)	2714 (55.9)	1152 (57.7)	6345 (56.4)	
Chronic pain Diagnosis	460 (10.5)	582 (12.0)	219 (11.0)	1261 (11.2)	0.071
Fibromyalgia Diagnosis	232 (5.3)	241 (5.0)	113 (5.7)	586 (5.2)	0.476
Home opioid, within 90 days of surgery	799 (18.2)	658 (13.5)	262 (13.1)	1719 (15.3)	<0.001
Operating theatre time	6.2 (5.2–7.5)	6.8 (5.6–8.1)	6.4 (5.2–7.8)	6.4 (5.3–7.8)	<0.001
Local anaesthetic, administered by surgical team	464 (10.6)	242 (5.0)	111 (5.6)	817 (7.3)	<0.001
Preoperative Antiemetics	233 (5.3)	154 (3.2)	102 (5.1)	489 (4.3)	<0.001
Preoperative non-opioid analgesic*	1977 (45.1)	4023 (82.8)	1692 (84.7)	7693 (68.4)	<0.001
Regional block	659 (15.0)	1344 (27.7)	248 (12.4)	2251 (20.0)	<0.001
Intraoperative antiemetic Administration					
Dexamethasone	1991 (45.4)	4304 (88.6)	1710 (85.6)	8005 (71.2)	<0.001
Droperidol	736 (16.8)	407 (8.4)	930 (46.6)	2073 (18.4)	<0.001
Granisetron	1542 (35.2)	3808 (78.4)	1569 (78.6)	6919 (61.5)	<0.001
Haloperidol	266 (6.1)	2458 (50.6)	361 (18.1)	3085 (27.4)	<0.001
Ondansetron	629 (14.3)	340 (7.0)	78 (3.9)	1047 (9.3)	<0.001
Other antiemetics	22 (0.5)	41 (0.8)	10 (0.5)	73 (0.6)	0.081
Intraoperative non-opioid analgesic					
Acetaminophen	1409 (32.1)	3131 (64.4)	1012 (50.7)	5552 (49.4)	<0.001
Ketamine	2513 (57.3)	3092 (80.3)	1797 (90.0)	8212 (73.0)	<0.001
Procedure type					
CABG	1512 (34.5)	1663 (34.2)	627 (31.4)	3802 (33.8)	0.040
Valve	2780 (63.4)	2901 (59.7)	1212 (60.7)	6893 (61.3)	0.001
CABG + valve	573 (13.1)	484 (10.0)	208 (10.4)	1265 (11.3)	<0.001
Congenital - ACHD	379 (8.6)	502 (10.3)	146 (7.3)	1027 (9.1)	<0.001
Aortic	540 (12.3)	859 (17.7)	290 (14.5)	1689 (15.0)	<0.001
Thoracic	26 (0.6)	21 (0.4)	10 (0.5)	57 (0.5)	0.554
MAZE	326 (7.4)	236 (4.9)	111 (5.6)	673 (6.0)	<0.001
Other procedures	1203 (27.4)	1316 (27.1)	593 (29.7)	3112 (27.7)	0.080

analyses were conducted for the same primary, secondary, and exploratory outcomes for two subgroups: patients with high risk of postoperative pain (i.e. diagnosis of chronic pain or fibromyalgia, home opioid use 90 days before surgery) and patients undergoing isolated valve surgery. These analyses were added at the suggestion of reviewers. Analyses including selection of predictors, outcomes, and covariates were decided *a priori*. *P*-values <0.05 were considered statistically significant. All analyses were conducted using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). This manuscript adheres to the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) protocol (Supplementary Material 1).

Results

Descriptive statistics

There were 12 017 adults who underwent cardiac surgery with CPB from 2018 to 2023 (Fig. 1). There were 775 patients excluded (6.4%) because of duplicate patients (*n*=166), patients with no intraoperative opioids administered or documented (*n*=40), patients who died in the OR (*n*=7), and patients undergoing solid organ transplantation (*n*=562), resulting in an analytic sample of 11 242 patients (93.6%). Of the sample analysed, 17.8% of patients received methadone as the sole intraoperative opioid (Group M; *n*=1997), 43.2% of patients received methadone and another opioid (Group M+O; *n*=4859),

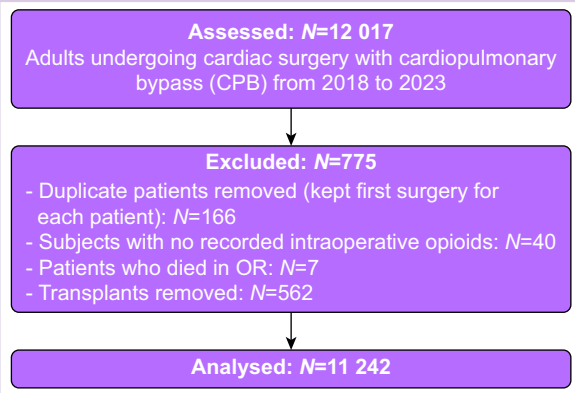

Fig 1. Flow chart.

most commonly, fentanyl (99.8%), and 39.0% of patients did not receive methadone (Group O; n=4386). The number of subjects with daily pain score and OME observations varied, primarily because of varying LOS. Patient characteristics are shown in Table 1.

Three patients had unknown BMI because of missing height measurements; BMI was computed using their observed weight and the mean height of their respective sex. Some 24 subjects (0.2%) had unassessed smoking statuses, who were added to the 'never smoker' group. No missing values were present in any of the other covariates.

The cohort for this study had a median age of 65.0 yr (IQR=55.0–72.0 yr) with statistically significant differences between the groups (P<0.001). Group O had a median age of 65.0 yr (IQR=56.0–72.0 yr), Group M+O and Group M both had a median age of 64.0 yr (IQR=54.0–71.0 yr). The median BMI was 28.4 (IQR=25.0–32.7), with Group O having a lower BMI (median BMI=28.1, IQR=24.8–32.2) compared with Group M+O (BMI=28.7, IQR=25.2–33.0) and Group M (median BMI=28.6, IQR=25.1–32.9; P<0.001). Most patients were male (67.4%) and there were no differences in gender by groups (P=0.528). The median Charlson Comorbidity Index was 4 (IQR=3–6). There were no differences in history of chronic pain (11.2%) or fibromyalgia (5.2%) by group (P=0.071 and P=0.476, respectively). Patients in Groups M and M+O were less likely to have an opioid listed on their home medications within 90 days before surgery (Group M=13.1%; Group M+O=13.5%; Group O=18.2%; P<0.001).

The median length of surgery was 6.4 h (IQR=5.3–7.8). The majority of patients underwent isolated valve procedures (n=6893, 61.3%); 34% of patients underwent coronary artery bypass grafts (CABG, 33.8%, n=3802), and there were differences in surgical procedures by group (P<0.05). Twenty percent of patients received regional blocks (n=2251), 7.3% received local anaesthetics intraoperatively from the surgical team (n=817), 4.3% received preoperative antiemetics (n=489), and 81.2% received one or more antiemetics intraoperatively (n=9128).

Primary outcome

Overall, daily pain scores peaked on POD1, with a median score of 2.1 (IQR=0.1–3.4) and decreased to a median of 1.3 by POD7 (Table 2; Fig. 2). Both Group M and Group M+O had lower

Table 2 Daily mean pain scores, stratified by methadone administration. Models adjusted for age, BMI, sex, year of surgery, Charlson Comorbidity Index, smoking status, history of chronic pain, diagnosis of fibromyalgia, use of home opioid within 90 days of surgery, administration of antiemetics and non-opioid analgesics before surgery, intraoperative administration of antiemetics and non-opioid analgesics, preoperative or intraoperative regional block, use of local anaesthetic by surgical team, length of surgery (i.e. OR time), and surgery type. IQR, inter-quartile range.

Outcome	n	Group	Median (IQR)	Coefficient	95% Lower	95% Upper	P-value
Mean pain score day 0	10 935	M+O	1.1 (0.0–2.5)	β=−0.77	−0.88	−0.65	<0.001
		M	1.2 (0.0–2.4)	β=−0.71	−0.85	−0.57	<0.001
		O	2.1 (0.1–3.4)	Reference			
Mean pain score day 1	11 222	M+O	2.5 (1.5–3.4)	β=−0.55	−0.64	−0.45	<0.001
		M	2.3 (1.4–3.2)	β=−0.58	−0.69	−0.47	<0.001
		O	2.8 (1.9–3.7)	Reference			
Mean pain score day 2	11 201	M+O	2.1 (1.3–3.0)	β=−0.32	−0.41	−0.24	<0.001
		M	2.0 (1.2–2.8)	β=−0.32	−0.42	−0.22	<0.001
		O	2.3 (1.5–3.1)	Reference			
Mean pain score day 3	11 179	M+O	1.6 (0.8–2.4)	β=−0.28	−0.37	−0.19	<0.001
		M	1.5 (0.8–2.4)	β=−0.27	−0.37	−0.17	<0.001
		O	1.8 (1.0–2.7)	Reference			
Mean pain score day 4	10 765	M+O	1.2 (0.5–2.2)	β=−0.22	−0.30	−0.15	<0.001
		M	1.3 (0.5–2.1)	β=−0.22	−0.31	−0.12	<0.001
		O	1.6 (0.7–2.4)	Reference			
Mean pain score day 5	9295	M+O	1.1 (0.4–2.1)	β=−0.27	−0.37	−0.16	<0.001
		M	1.2 (0.4–2.1)	β=−0.28	−0.40	−0.17	<0.001
		O	1.5 (0.6–2.5)	Reference			
Mean pain score day 6	6907	M+O	1.1 (0.3–2.1)	β=−0.28	−0.41	−0.14	<0.001
		M	1.1 (0.3–2.1)	β=−0.33	−0.49	−0.18	<0.001
		O	1.4 (0.5–2.4)	Reference			
Mean pain score day 7	4984	M+O	1.0 (0.2–2.1)	β=−0.23	−0.36	−0.10	0.002
		M	1.1 (0.2–2.0)	β=−0.20	−0.36	−0.005	0.008
		O	1.3 (0.3–2.3)	Reference			

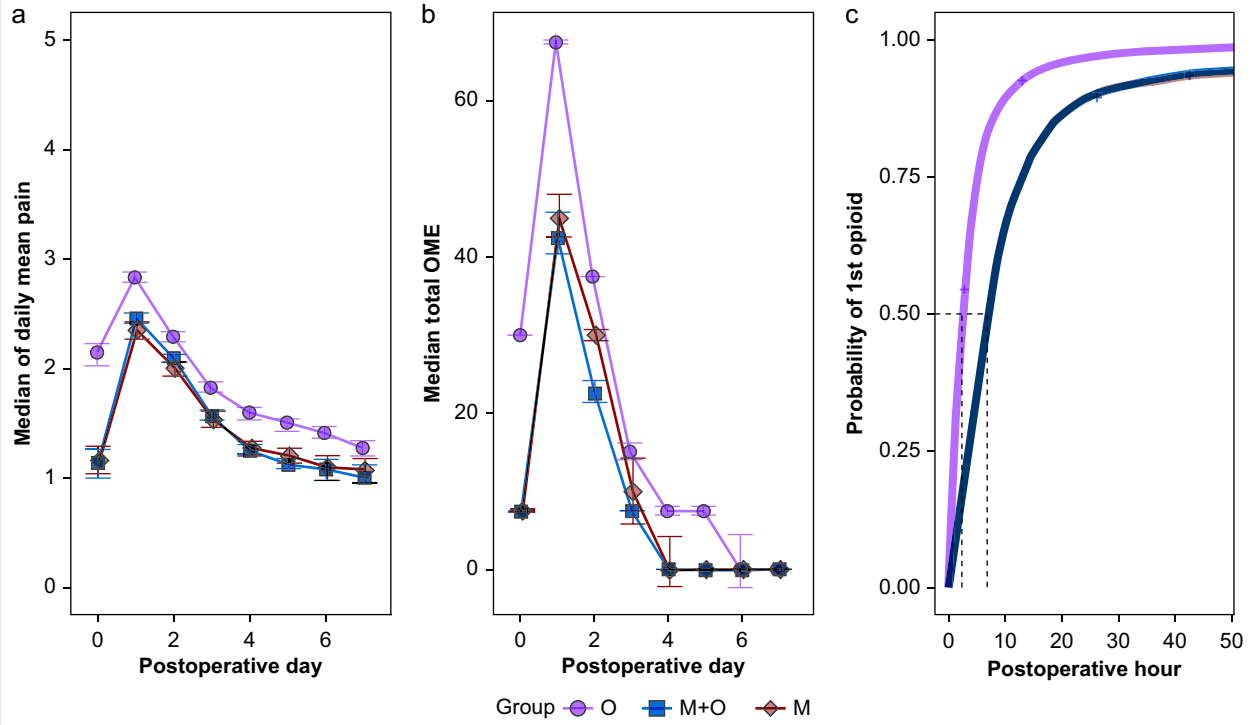

Fig 2. Postoperative pain and ICU opioid administration. Error bars represent 95% confidence intervals from bootstrapping. OME, oral morphine equivalents.

daily mean pain scores than Group O for all days from POD0 to POD7 after adjusting for covariates (all $P<0.01$). The greatest difference was observed on POD0; coefficients from this model estimated that Group M+O had a median 0.77 lower than that of Group O (95% confidence interval [CI]: −0.88 to −0.65), and Group M had a median 0.71 lower than Group O (95% CI: −0.85 to −0.57).

Secondary outcomes

Overall, daily total OME also peaked on POD1 with a median of 67.5 morphine milligram equivalents (MME) (IQR=37.5–105.0) and decreased to 0 MME by POD7 (IQR=0.0–15.0; Table 3, Fig. 2). After adjusting for covariates, both Groups M and Group M+O had lower total OME than Group O for all days POD0 to POD6 (all $P<0.001$); no difference was observed on POD7. The median number of hours until initial postoperative opioid administration after surgery was 2.55 h (IQR=1.07–5.12 h), 6.82 h (IQR=3.52–12.98 h), and 7.00 h (IQR=3.82–12.95 h) for Group O, Group M+O, and Group M, respectively (Fig. 2). After adjusting for covariates, the hazard ratio for time to first postoperative opioid administration was 0.50 (95% CI: 0.49–0.55; $P<0.001$) and 0.51 (95% CI: 0.48–0.55; $P<0.001$) for Group M+O, and Group M, respectively.

Exploratory outcomes

Overall, pruritis was observed in 0.8% of patients with no difference by group (Table 4). Postoperative urinary retention was observed in 2.8% ($n=121$), 6.9% ($n=337$), and 4.3% ($n=85$) of patients from Group O, Group M+O, and Group M, respectively. After covariate adjustment, there were no statistically significant differences in urinary retention by group. The preoperative to postoperative change in QTc interval was 3.85 ms less in Group M+O compared with Group O after adjusting for covariates ($P=0.017$); no significant difference was observed when comparing preoperative and postoperative QTc for Group M compared with Group O ($P=0.936$). ICU LOS was significantly lower in Groups M+O (median: 1.2 days, IQR=0.9–2.8 days) compared with Group O (median: 5.3 days, IQR=3.0–12.4 days) (ß=−0.14; $P<0.001$), however, there were no statistically significant differences in time to tracheal extubation, incidence of reintubation, naloxone administration, or PONV.

Sensitivity analyses

The analyses were repeated among patients at higher risk for poor pain outcomes ($n=2777$) and patients who underwent isolated valve surgery ($n=2771$); the descriptive data are included in Supplementary Table S1.

Primary outcome

The results for the sensitivity analyses were similar to the primary analyses; for both subgroups pain scores peaked on POD1 (Supplementary Table S2). For the high-risk pain patients, Groups M and Group M+O had lower postoperative pain scores until POD3 and for the isolated valve surgery patients until POD2. Postoperative pain scores were lower in both

Table 3 Postoperative opioid usage, stratified by methadone administration. Models adjusted for age, BMI, sex, year of surgery, Charlson Comorbidity Index, smoking status, history of chronic pain, diagnosis of fibromyalgia, use of home opioid within 90 days of surgery, administration of antiemetics and non-opioid analgesics before surgery, intraoperative administration of antiemetics and non-opioid analgesics, preoperative or intraoperative regional block, use of local anaesthetic by surgical team, length of surgery (i.e. OR time), and surgery type. HR, hazard ratio; IQR, inter-quartile range; OME, oral morphine equivalents.

Outcome	Model *n*	Group	Median (IQR)	Model estimate	95% Lower	95% Upper	*P*-value
Hours to first postoperative opioid	11 238	M+O	6.82 (3.52–12.98)	HR=0.50	0.49	0.55	<0.001
		M	7.00 (3.82–12.95)	HR=0.51	0.48	0.55	<0.001
		O	2.55 (1.07–5.12)	Reference			
Total OME day 0	11 142	M+O	7.5 (0.0–22.5)	β=−16.75	−17.89	−15.60	<0.001
		M	7.5 (0.0–19.0)	β=−16.58	−17.92	−15.24	<0.001
		O	30.0 (7.5–53.0)	Reference			
Total OME day 1	11 105	M+O	42.5 (15.5–75.0)	β=−24.19	−27.27	−21.11	<0.001
		M	45.0 (15.0–79.0)	β=−23.51	−27.11	−19.92	<0.001
		O	67.5 (37.5–105.0)	Reference			
Total OME day 2	11 163	M+O	22.5 (7.5–52.5)	β=−11.10	−13.56	−8.64	<0.001
		M	30.0 (7.5–60.0)	β=−10.20	−13.07	−7.34	<0.001
		O	37.5 (15.0–67.5)	Reference			
Total OME day 3	11 092	M+O	7.5 (0.0–30.0)	β=−5.38	−6.62	−4.14	<0.001
		M	10.0 (0.0–34.4)	β=−4.94	−6.38	−3.50	<0.001
		O	15.0 (0.0–45.0)	Reference			
Total OME day 4	10 737	M+O	0.0 (0.0–16.0)	β=−2.59	−3.35	−1.83	<0.001
		M	0.0 (0.0–22.5)	β=−3.02	−3.90	−2.15	<0.001
		O	7.5 (0.0–30.0)	Reference			
Total OME day 5	9401	M+O	0.0 (0.0–15.0)	β=−2.35	−2.95	−1.74	<0.001
		M	0.0 (0.0–15.0)	β=−2.63	−3.32	−1.93	<0.001
		O	7.5 (0.0–22.5)	Reference			
Total OME day 6	7345	M+O	0.0 (0.0–11.5)	β=−0.73	−1.15	−0.32	<0.001
		M	0.0 (0.0–15.0)	β=−0.85	−1.33	−0.37	<0.001
		O	0.0 (0.0–22.5)	Reference			
Total OME day 7	5634	M+O	0.0 (0.0–8.0)	β=−0.00	−5.15	5.15	
		M	0.0 (0.0–9.5)	β=−0.00	−6.01	6.01	1.000
		O	0.0 (0.0–15.0)	Reference			

Groups M and M+O from POD3 (and POD4) until POD7 but this was not statistically significant. Similar to the primary analyses, the greatest difference was observed on POD0; coefficients from this model estimated that Group M+O had a median 0.75 lower than that of Group O (95% CI: −1.04 to −0.46), and Group M had a median 0.73 lower than Group O (95% CI: −1.07 to −0.39) for high-risk pain patients. For patients undergoing isolated valve surgery, Group M+O had a median 0.84 lower than that of Group O (95% CI: −1.04 to −0.63), and Group M had a median 0.78 lower than Group O (95% CI: −1.02 to −0.53) for POD0.

Secondary outcomes

Daily total OME was lower in both Groups M and M+O for high-risk pain patients until POD2 and until POD5 for patients undergoing isolated valve surgery (Supplementary Table S3). The hazard ratio for hours to first postoperative opioid was similar in magnitude and statistically significant for both patient subgroups.

Exploratory outcomes

There were some differences in exploratory outcomes in the subgroups compared with the primary analyses (Table 4). The clinically significant findings include increased hospital LOS. Although the median hospital LOS is lower for both methadone groups, after adjusting for covariates, there were longer hospital LOS for Group M for both the high-risk pain patients (β=1.17; *P*<0.001) and patients undergoing isolated valve surgery (β=0.48; *P*<0.001), although there were no differences in ICU LOS. There were also higher odds of PONV for both methadone groups among patients undergoing isolated valve surgery.

Discussion

Postoperative pain control is a challenging problem in cardiac surgery patients. Not only is pain often underrecognised and undertreated in these patients, but treatment itself with intermittent opioid administration can have significant adverse effects.[17] Administration of methadone in cardiac surgery to improve postoperative pain control has shown promise.[10] In this retrospective cohort study, we analysed outcomes of 11 967 patients who underwent cardiothoracic surgery between 2018 and 2023 at four Mayo Clinic hospitals. We observed several notable benefits among those who received methadone during surgery, whether alone or in combination with other opioids.

In a systematic review (four studies; *n*=435), administration of intraoperative methadone in cardiothoracic surgery led to a significant reduction of postoperative pain scores and opioid utilisation in the first 24 h after surgery.[10] Similar results were demonstrated in a prospective double-blind, randomised, controlled trial in which the administration of methadone (0.3 mg kg^{-1}) compared with fentanyl (12 μg kg^{-1}) during cardiothoracic surgery resulted in significant reductions in postoperative opioid requirements and improvements in pain scores for 72 h after extubation.[9] Our study not only exhibited

Table 4 Exploratory outcomes regression model, stratified by methadone administration. Models adjusted for age, BMI, gender, year of surgery, Charlson comorbidity index, smoking status, history of chronic pain, diagnosis of fibromyalgia, use of home opioid within 90 days of surgery, administration of antiemetics and non-opioid analgesics before surgery, intraoperative administration of antiemetics and non-opioid analgesics, preoperative or intraoperative regional block, use of local anaesthetic by surgical team, length of surgery (i.e. OR time), and surgery type. PONV, postoperative nausea and vomiting.

Outcome	Model *n*	Group	Value	Model estimate	95% Lower	95% Upper	*P*-value
Change in QTc	7501	M+O	31.5 (47.1)	β=−3.85	−7.01	−0.68	0.017
		M	32.8 (48.2)	β=−0.15	−3.53	3.84	0.936
		O	36.7 (51.1)	Reference			
Pruritus, *n* (%)	11 242	M+O	46 (0.9)	OR=1.60	0.85		0.148
		M	14 (0.7)	OR=1.35	0.62	2.96	0.448
		O	33 (0.8)	Reference			
Urinary retention, *n* (%)	11 242	M+O	337 (6.9)	OR=1.29	0.96	1.74	0.095
		M	86 (4.3)	OR=1.14	0.79	1.63	0.488
		O	121 (2.8)	Reference			
Time to extubation (h)	11 189	M+O	4.5 (2.4–8.0)	β=0.27	0.02	0.52	0.036
		M	4.7 (2.8–7.9)	β=0.25	−0.04	0.54	0.092
		O	5.3 (3.0–12.4)	Reference			
ICU length of stay (days)	11 242	M+O	1.2 (0.9–2.8)	β=−0.14	−0.21	−0.07	<0.001
		M	1.5 (0.9–2.9)	β=−0.06	−0.14	0.02	0.133
		O	2.1 (1.1–4.0)	Reference			
Hospital length of stay (days)	11 242	M+O	6.4 (5.3–9.4)	β=0.12	−0.06	0.31	0.185
		M	7.2 (5.4–10.3)	β=0.50	0.29	0.72	<0.001
		O	7.3 (5.4–11.0)	Reference			
PONV, *n* (%)	11 242	M+O	2595 (53.4)	OR=1.12	0.99	1.27	0.068
		M	1148 (57.5)	OR=1.13	0.98	1.31	0.093
		O	2647 (60.4)	Reference			
Postoperative naloxone, *n* (%)	11 242	M+O	49 (1.0)	OR=1.68	0.92		0.090
		M	23 (1.2)	OR=1.66	0.83	3.31	0.154
		O	41 (0.9)	Reference			
Reintubation		M+O	141 (2.9)	OR=0.90	0.65	1.24	0.505
		M	76 (3.8)	OR=1.15	0.80	1.65	0.456
		O	227 (5.2)	Reference			

similar findings in the immediate postoperative period, but we also found significant analgesic benefits of methadone extended through POD7 as evidenced by lower reported mean pain scores and reduced opioid administration. Although the difference in pain scores is not clinically significant (0.71–0.77 lower), lower pain scores in the context of lower OME demonstrates that the reduction in opioids did not result in worse pain control and this is clinically very relevant. The use of methadone in an enhanced recovery after surgery (ERAS) programme will contribute to marginal gains, and the accumulation of these marginal gains leads to improvement in clinical outcomes.[18,19] Although improved postoperative analgesia with methadone is not a novel finding, our study is the first, to our knowledge, to demonstrate decreased pain scores and decreased opioid utilisation for a notably extensive duration of 7 and 6 days after surgery, respectively. The sensitivity analyses among patients at high risk of postoperative pain and patients undergoing isolated valve surgery were mostly consistent in the magnitude of effect, but were not statistically significant beyond POD2 and POD3. The difference in statistical significance may be a true difference or may reflect the lower sample size in the subgroups (~25% of the sample) in the context of several covariates.

Methadone is advantageous for its unique pharmacokinetic properties including a quick equilibration half-life of 8 min and a long elimination half-life of 24–36 h.[8,9] However, improved analgesia lasting through POD7 was an unanticipated outcome. This encouraging finding may be the result of methadone's additional activity as an NMDA receptor antagonist. This unique property decreases the risk of developing opioid tolerance and hyperalgesia caused by overactivation of the NMDA receptor pathway.[20] The administration of methadone during cardiac surgery may not only improve acute postoperative pain, but it may also reduce the risk of chronic post-sternotomy pain and decrease risk of developing opioid use disorder.[10]

Few postoperative complications were observed with intraoperative methadone compared with other opioids. In a prior study, there was no significant difference in pruritis, urinary retention, PONV, naloxone administration, nor reintubation in which authors concluded that intraoperative methadone resulted in decreased postoperative pain but also did not have distinguishable side-effects compared with morphine.[16] The change in QTc in the methadone only group was not statistically different than the change in QTc in the no methadone group, however, the methadone plus other opioid group had a decrease in QTc after surgery compared with before surgery. There were small differences in the time to extubation, ICU LOS, and hospital LOS between groups; the methadone plus other opioid group had a statistically significant but not clinically significant longer time to extubation, however, there was a shorter but not clinically significant difference in ICU LOS for the methadone plus other opioid group compared with the no methadone group. There was also a statistically longer hospital LOS for the methadone group compared with the no methadone group, but this was not clinically significant. There were some statistically but unlikely clinically significant differences in hospital LOS for the sensitivity analyses and higher odds of PONV for Group M in the subgroups.

Although the results of this study certainly support the use of methadone for cardiac surgery,[21] it is imperative to ask why methadone administration in cardiac surgery is not a widespread practice.[11,22] Unfamiliarity, public stigma, and hospital restrictions all likely contribute to the slow adoption of use. A recent pro-con debate suggested that unknowns regarding the side-effect profile may limit its use, combined with uncertainty with dosing of methadone.[21] This study included a wide range of patients with varying comorbidities without an increase in side-effects compared with shorter-acting opioids. There may be some degree of bias in patient selection with regards to choosing the appropriate candidate for methadone combined with the anaesthesiologist's familiarity with methadone. Administration of balanced anaesthesia with multimodal analgesia has become a core principle of perioperative care and ERAS initiatives aimed to improve patient outcomes.[23] The utilisation of methadone in cardiac surgery increased over time in this study, which coincides with the advent of enhanced recovery pathways and advancements in surgical techniques.[24–26] Use of methadone in conjunction with implementation of these patient-centred pathways may enhance cardiac surgical outcomes.[22] Additionally, patients with increased illness severity, as evidenced by ASA physical status classification 5 and higher Charlson Comorbidity Index, were less likely to receive methadone; however, there was no difference in age, sex, and chronic pain syndromes or fibromyalgia diagnoses among those who received methadone for cardiac surgery. Further investigation is warranted to assess if patients with an increased illness severity may also benefit from the use of methadone.

Strengths and limitations

This study is an important addition to the literature as it identifies differences in intraoperative management by patient characteristics. Additionally, it includes a large sample of patients at different sites within a single medical system which reduces differences in management and hospital practices which are of concern for national and multicentre studies. Another strength is the multidisciplinary team that conducted this study including cardiothoracic anaesthesiologists at different stages of their careers, a cardiac surgeon, an intensivist, and two medical students pursuing anaesthesiology. Nonetheless, several limitations should be noted. First, our research was conducted within a single hospital system, which may limit the generalisability of our findings. Different centres have varied patient characteristics, surgical methodologies, and perioperative protocols that could influence outcomes. Our results are not universally applicable without further validation from multicentre studies. Relatedly, patients remaining in the ICU longer (pain and OME data until POD7) are likely different than the patients discharged earlier, which also threatens generalisability. Additionally, the retrospective nature of our study has inherent limitations, as available outcomes for analysis are limited to the data contained in the electronic medical record (EMR) and the inability to account for the effect of practice changes and other confounders in the analysis. Our main outcome, pain score, although widely utilised in research studies, is a subjective measure. Despite the limitations of a retrospective study design and the potential for a high risk of bias,[10] retrospective studies can add to the literature by including large, pragmatic samples with few exclusion criteria that are generalisable to patients undergoing cardiac surgery. Additionally, we attempted to address sources of biases based on the study design by clearly defining our outcome and predictor variables, controlling for important confounders, and discussing the pattern of missing data. However, randomised prospective studies are needed to confirm these findings.

Conclusions

Immense opportunity exists to enhance the perioperative care of cardiac surgical patients. Although the findings of our study are promising, further investigation is needed in the form of multicentre, prospective randomised controlled trials to better define the role of methadone in cardiac surgery. Future research should also focus on optimal dosing, timing, and individualised approaches with other opioids, adjuncts, and regional anaesthetics to improve outcomes in this population. Our data support the need for further investigation and innovation with regards to the use of methadone in enhanced recovery protocols to improve patient outcomes and quality of life after cardiac surgery.

Author's contributions

Contributed to the preparation of the manuscript and approved the final version: all authors
Study conception and design: JNE, MAW, BBS, AJM
Data extraction: ERP
Data analysis: SABP
Interpretation of the data: JNE, MAW, BBS, SABP, AJM
Drafting of the manuscript: JNE, MAW, BBS, SABP, ERP, AJM
Revision of the manuscript: JNE, MAW, BBS, ERP, AJM
Helped write and critically revise the manuscript for important intellectual content: MKF, OD, KAS-D, EDW
Approved the final version of the manuscript: MKF, OD, KAS-D, EDW
Final approval of the manuscript: JNE, MAW, BBS, SABP, ERP, AJM
Agree to be accountable for all aspects of this work: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

We would like to acknowledge Mohanad R. Youssef, MD for his help with formatting and submission of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2024.100270.

References

1. Santa Cruz Mercado LA, Liu R, Bharadwaj KM, et al. Association of intraoperative opioid administration with postoperative pain and opioid use. *JAMA Surg* 2023; **158**: 854–64
2. Wehrfritz A, Senger A-S, Just P, et al. Patient-controlled analgesia after cardiac surgery with median sternotomy: no advantages of hydromorphone when compared to morphine. *J Cardiothorac Vasc Anesth* 2022; **36**: 3587–95

3. Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chioléro R, von Segesser LK. Pain location, distribution, and intensity after cardiac surgery. *Chest* 2000; **118**: 391–6
4. Guimarães-Pereira L, Reis P, Abelha F, Azevedo LF, Castro-Lopes JM. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 2017; **158**: 1869–85
5. Daoust R, Paquet J, Cournoyer A, et al. Side effects from opioids used for acute pain after emergency department discharge. *Am J Emerg Med* 2020; **38**: 695–701
6. Chung CP, Callahan ST, Cooper WO, et al. Individual short-acting opioids and the risk of opioid-related adverse events in adolescents. *Pharmacoepidemiol Drug Saf* 2019; **28**: 1448–56
7. Shoar S, Esmaeili S, Safari S. Pain management after surgery: a brief review. *Anesth Pain Med* 2012; **1**: 184–6
8. Murphy GS, Szokol JW. Intraoperative methadone in surgical patients: a review of clinical investigations. *Anesthesiology* 2019; **131**: 678–92
9. Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative methadone for the prevention of postoperative pain: a randomized, double-blinded clinical trial in cardiac surgical patients. *Anesthesiology* 2015; **122**: 1112–22
10. Lobova VA, Roll JM, Roll MLC. Intraoperative methadone use in cardiac surgery: a systematic review. *Pain Med* 2021; **22**: 2827–34
11. Wang L, Yang M, Meng W. Prevalence and characteristics of persistent postoperative pain after thoracic surgery: a systematic review and meta-analysis. *Anesth Analg* 2023; **137**: 48–57
12. Burtoft MA, Gillespie SM, Laporta ML, et al. Postoperative nausea and vomiting and pain after robotic-assisted mitral valve repair. *J Cardiothorac Vasc Anesth* 2020; **34**: 3225–30
13. Carvalho AC, Sebold FJG, Calegari PMG, Oliveira BH de, Schuelter-Trevisol F. Comparison of postoperative analgesia with methadone versus morphine in cardiac surgery. *Braz J Anesthesiol* 2018; **68**: 122–7
14. Udelsmann A, Maciel FG, Servian DCM, Reis E, de Azevedo TM, Melo M de S. Methadone and morphine during anesthesia induction for cardiac surgery. Repercussion in postoperative analgesia and prevalence of nausea and vomiting. *Rev Bras Anestesiol* 2011; **61**: 695–701
15. Robinson JD, Caruso TJ, Wu M, Kleiman ZI, Kwiatkowski DM. Intraoperative methadone is associated with decreased perioperative opioid use without adverse events: a case-matched cohort study. *J Cardiothorac Vasc Anesth* 2020; **34**: 335–41
16. Kendall MC, Alves LJ, Pence K, Mukhdomi T, Croxford D, De Oliveira GS. The effect of intraoperative methadone compared to morphine on postsurgical pain: a meta-analysis of randomized controlled trials. *Anesthesiol Res Pract* 2020; **2020**, 6974321
17. Jayakumar S, Borrelli M, Milan Z, Kunst G, Whitaker D. Optimising pain management protocols following cardiac surgery: a protocol for a national quality improvement study. *Int J Surg Protoc* 2019; **14**: 1–8
18. Leng JC, Mariano ER. A little better is still better: using marginal gains to enhance 'enhanced recovery' after surgery. *Reg Anesth Pain Med* 2020; **45**: 173–5
19. Rosner L, Gonzalez M. Marginal gain, does it matter? *J Thorac Dis* 2019; **11**: S1313–6
20. Gutwinski S, Schoofs N, Stuke H, Riemer TG, Wiers CE, Bermpohl F. Opioid tolerance in methadone maintenance treatment: comparison of methadone and levomethadone in long-term treatment. *Harm Reduct J* 2016; **13**: 7
21. D'Souza RS, Esfahani K, Dunn LK. Pro-con debate: role of methadone in enhanced recovery after surgery protocols—superior analgesic or harmful drug? *Anesth Analg* 2023; **137**: 76
22. Makkad B, Heinke TL, Sheriffdeen R, et al. Practice advisory for preoperative and intraoperative pain management of thoracic surgical patients: Part 1. *Anesth Analg* 2023; **137**: 2–25
23. Grant MC, Chappell D, Gan TJ, et al. Pain management and opioid stewardship in adult cardiac surgery: joint consensus report of the PeriOperative quality initiative and the enhanced recovery after surgery cardiac society. *J Thorac Cardiovasc Surg* 2023; **166**. 1695–706.e2
24. Bainbridge D, Cheng D. Current evidence on fast track cardiac recovery management. *Eur Heart J Suppl* 2017; **19**. A3–7
25. MacLeod JB, D'Souza K, Aguiar C, et al. Fast tracking in cardiac surgery: is it safe? *J Cardiothorac Surg* 2022; **17**: 69
26. Steinmetz C, Bjarnason-Wehrens B, Walther T, Schaffland TF, Walther C. Efficacy of prehabilitation before cardiac surgery: a systematic review and meta-analysis. *Am J Phys Med Rehabil* 2023; **102**: 323–30

Handling editor: Phil Hopkins