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REVIEW

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The influence of preoperative or intraoperative methadone on postcardiac surgery pain and opioid administration: a systematic review and meta-analysis

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Abstract

Background Opioid analgesia remains a cornerstone of the management of perioperative pain in cardiac surgical patients. Emerging evidence suggests that intermediate and long-term postoperative opioid dependence is underappreciated and associated with adverse patient outcomes. Methadone has emerged in the cardiothoracic and non-cardiothoracic anesthesia literature as an option that may provide lasting analgesic benefit and may be associated with a reduction in overall perioperative opioid requirements.

Main body This study was a systematic literature review and meta-analysis that aimed to provide evidence supporting the use of perioperative or intraoperative methadone in adult cardiac surgical patients, particularly with respect to objective measures of postoperative pain and opioid requirements prior to and at discharge from the hospital. Electronic searches of three research databases were performed: PubMed (1972 to October 2023), Ovid MEDLINE (1946 to October 2023), and EMBASE (1978 to October 2023). This search yielded a total of 190 articles, 7 of which met the relevant inclusion and exclusion criteria. This included five randomized controlled trials and two large retrospective cohort studies.

Conclusion Preoperative or intraoperative methadone led to reduced pain scores at 24 h postoperatively and reduced opioid requirements at discharge. Methadone may be effective at reducing perioperative pain scores and opioid requirements postoperatively, including at discharge. The literature on this subject has important limitations, and further research in larger randomized controlled trials is needed.

Keywords Cardiac surgery, Pain management, Perioperative management, Sternotomy

Background

Cardiac surgery remains integral in the management of cardiovascular disease. In Australia, 15,712 cardiac surgical procedures were performed in 2021, and the majority of these procedures were performed via median sternotomy [1]. Although median sternotomy is often well tolerated, acute and chronic pain remain significant challenges. Opioid analgesia remains an integral part of postoperative care for patients undergoing cardiac surgery; this has been largely unchanged since the emergence of opioid-based

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anesthesia for cardiovascular surgery in the 1960s [2]. Although opioids provide effective pain relief in the perioperative period, there are numerous established harms associated with their use. As such, there has been a recent move toward multimodal opioid-sparing analgesia techniques in both cardiac and thoracic surgery [2].

A recent report by the Enhanced Recovery After Surgery Cardiac Society published in 2023 recommended against the routine use of high-dose opioid analgesia for patients undergoing cardiac surgery [2]. High-dose opioids are associated with prolonged mechanical ventilation, delirium, nausea and vomiting, and constipation [2]. An emerging concern is the risk of intermediate and long-term dependence and abuse [2]. A recent Australian single-center retrospective cohort of 2205 patients from 2012 to 2019 revealed that 76.4% of patients were prescribed oral opioids at discharge despite the majority of this cohort (60%) not requiring opioids in the 24 h prior to discharge [3]. Fourteen percent of patients received oral opioids at 3 to 12 months after their operation [3]. This finding of a persistent medium to long-term opioid requirement postcardiac surgery and sternotomy has been demonstrated in multiple other studies [2, 4–6]. Given the established adverse effects and sequelae of long-term opioid use, it is imperative to consider alternative strategies to reduce opioid requirements at discharge following cardiac surgery without impacting pain management during the perioperative period.

Methadone has emerged as an alternative agent that provides prolonged analgesia lasting 24 to 36 h, with the potential to reduce the requirement for short-acting opioids in the postoperative period [7, 8]. In addition to potent μ-receptor agonist activity, it acts on κ- and σ-opioid receptors while also preventing the reuptake of monoamines in the brain [7]. By modulating the reuptake of monoamines such as noradrenaline and serotonin in the central nervous system, methadone may reduce opioid sensitization and the development of chronic pain [7]. Methadone also inhibits NDMA receptors, which have been implicated in the development of sensitization and chronic pain[7, 8]. These pharmacological characteristics render methadone dually attractive as a long-acting agent with the capacity to reduce short-acting opioid requirements and to mitigate sensitization and reduce the probability of chronic pain. The veracity of these potential benefits warrants comprehensive, objective investigation. As such, this systematic review aimed to determine the effect of pre- or intraoperative administration of methadone on immediate postoperative pain scores and opioid requirements after cardiac surgery via median sternotomy.

Main text

A systematic review was completed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. Ethics approval was not required for this study.

Systematic search

Electronic searches of three research databases were performed: PubMed (1972 to October 2023), Ovid MEDLINE (1946 to October 2023), and EMBASE (1978 to October 2023). The literature search was completed on 10 October 2023. The search terms, including Boolean operators, were as follows: ((‘cardiac surgery’ OR ‘heart surgery’) OR (‘median sternotomy’ OR sternotomy’)) AND ‘methadone’. A manual search of references was also conducted. The articles were independently reviewed by two authors (JG and LC) in parallel, with disagreements resolved by either of the senior authors (WP).

Inclusion and exclusion

We included all studies examining the use of pre- or intraoperative methadone (either oral or intravenous) in patients aged 18 years and older who underwent cardiac surgery via median sternotomy. This included randomized controlled trials (RCTs) and observational studies.

We excluded any study that included patients under 18 years of age, studies involving animals and cardiac surgery not via median sternotomy (i.e., minimally invasive procedures including mini-thoracotomy, thoracotomy, and robotic-assisted surgery). Conference abstracts and non-English language manuscripts were excluded. We also excluded case reports and review articles.

Outcomes

The primary outcome of this review was the impact of methadone on postoperative pain scores at 24 h postoperatively. This was reported using various pain scales, including the Numeric Pain Rating Scale (NPRS), with 0 indicating no pain and 10 indicating the highest level of pain, the visual analog pain score (VAS), and the verbal rating scale (VRS).

Additional outcome measures included the effect of methadone on postoperative opioid requirements to discharge, the adverse effects of methadone administration compared to those of conventional opioid administration (morphine or fentanyl) and discharge opioid requirements (when reported). Additionally, we included any study with long-term follow-up beyond discharge.

Data extraction

The data were extracted by the first author by examining the relevant tables, text, and supplementary material of the included articles. Uncertainty was resolved by consensus with the second author. Any disagreements were then resolved by the senior author.

Assessment of bias

The included manuscripts were assessed for risk of bias by the second author, with uncertainty resolved by consensus with the first author. Any disagreements were then resolved by the senior author. The risk of bias in the included studies was systematically appraised using established frameworks; the five RCTs were assessed using version 2 of the Cochrane Collaboration's Risk of Bias tool for randomized trials (RoB 2) [10], while the two observational studies were assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool [11]. The bias assessment matrices are depicted in Tables 2 and 3 respectively.

Meta-analysis

For the primary outcome, a limited meta-analysis of three of the included RCTs was performed. Effect sizes were standardized using Cohen's *d* statistic considering variability in the pain assessment matrices used by the different authors. Due to anticipated heterogeneity, a random effects model was used to estimate the pooled effect size. Statistical analysis was performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The initial search of the three databases yielded 203 articles. After removal of duplicates, a total of 190 records were suitable for screening. The titles and abstracts of these articles were reviewed by two independent authors (redacted). After this, 177 articles were excluded because they did not fit the aforementioned inclusion criteria. A total of 13 articles were retrieved for review of the full text. A total of 7 articles remained, of which five were RCTs and two were large retrospective cohort studies [8–14]. The PRISMA diagram is shown in Fig. 1. One of the randomized controlled trials was a 12-month follow-up study from an original randomized controlled trial [8, 12].

Four RCTs, including a total of 336 patients, evaluated immediate postoperative outcomes [8, 12, 14, 15]. Three of these studies examined intravenous methadone administered intraoperatively, with one study evaluating preoperative oral methadone[8, 12, 14, 15]. The dose of methadone used varied among the studies from 0.1 to 0.3 mg/kg up to a maximum dose of 30 mg [8, 12, 14, 15]. One study used 20 mg intravenously for all patients rather than a weight-based regime [14]. The randomized controlled trial with pooled 12-month outcomes (pooled with spinal surgery patients, although cohorts reported separately) included 156 patients, with varying durations of follow-up [16]. The two observational studies included a total of 4443 patients[13, 17]. The studies are summarized in Table 1.

Risk of bias in individual studies

A full appraisal of each of the included studies according to the RoB 2 and ROBINS-I frameworks is provided in Tables 2 and 3, respectively. Of the RCTs, all excluding Murphy et al. had concerns about at least one of the reporting domains [8]. With respect to the observational studies, there was at least a moderate risk of bias in all cases. The principal limitations in both cases pertained to incomplete handling of confounders through a more robust statistical method such as propensity weighting, the selection bias inherent to their study designs, and the presence of significant differences in co-interventions (for example, stark differences in the concomitant administration of other analgesic agents).

Primary outcome: postoperative pain scores

The primary outcome of this systematic review was to evaluate the effect of pre- or intraoperative methadone on postoperative pain scores. All four of the randomized controlled trials reported outcome data in relation to this primary outcome. Three of the four studies reported lower postoperative pain scores at 12 to 24 h postoperatively [8, 12, 14]. The two observational studies provided mixed data, with the larger cohort study (Eisenbraun et al.) showing lower postoperative pain scores with methadone out to 72 h postoperatively [13, 17].

Murphy et al. reported that intraoperative methadone (dose 0.3 mg/kg up to a maximum of 30 mg) compared to fentanyl (12 µg/kg up to a maximum of 1200 µg) led to reduced postoperative pain scores using the NPRS scale [8]. At rest, this reduction was statistically significant at 72 h (2 vs 3, p=0.002) and was most pronounced at 8 h (2 vs 4, p<0.001) [8]. The level of pain associated with coughing was also significantly lower with methadone than with fentanyl, and this reduction was sustained for 72 h postoperatively (4 vs 5, p<0.001) [8]. This led to significantly better overall satisfaction with pain management in the methadone cohort (100% vs 90%, p<0.001) [8].

Bolton et al. compared preoperative oral methadone (a dose of 0.3 mg/kg up to a maximum of 30 mg) to a placebo in addition to the standard of care [15]. The authors reported pain scores for 72 h using the VRS [15]. There was a difference in the VRS at rest (2.8 vs 4) at 24 h

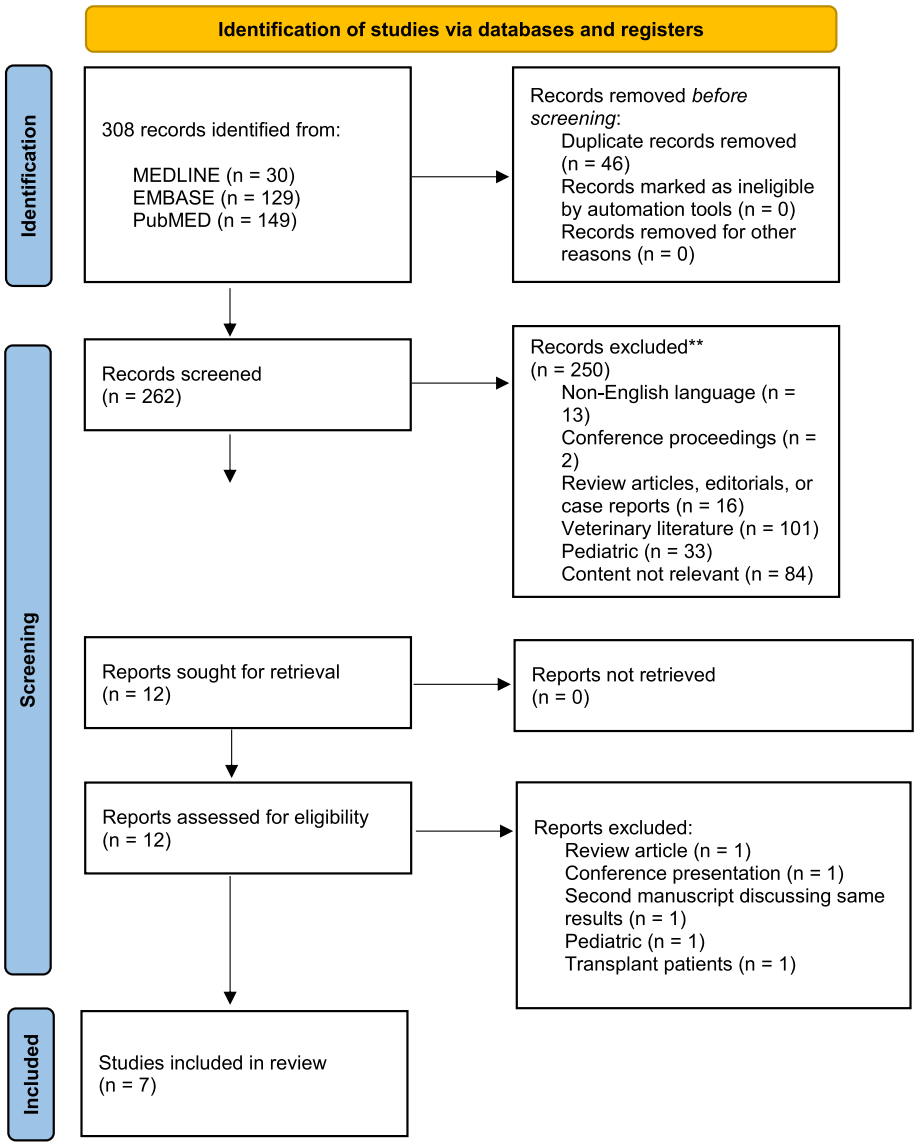

Fig. 1 PRISMA flow diagram

postoperatively but not with cough (4.8 vs 5.0) [15]. This difference was no longer present at 48 h (1.4 vs 1.4) or 72 h (1.3 vs 1.2) postoperatively [15].

Carvelho et al. compared intraoperative intravenous methadone (0.1mg/kg corrected weight) to intravenous morphine (0.1mg/kg corrected weight) given at the conclusion of anaesthesia [12]. The authors reported NPRS at 12, 24, and 36 h postoperatively [12]. There was no difference in the NPRS at 12 h (4.2 vs 4.7, p=0.186) or 36 h (0.5 vs 0.5, p=0.657) postoperatively [12]. However, there was an improvement in pain scores at 24 h postoperatively (1.9 vs 2.9, p=0.029) [12].

Udelsmann et al. compared intraoperative intravenous methadone (20 mg) to morphine (20 mg) [14]. The data are sparse, but the authors reported lower VAS scores at 24 h postoperatively[14].

For the primary outcome, a limited meta-analysis of three of the included RCTs was conducted. The principal limitations of this meta-analysis were the small sample sizes of the included studies and the heterogeneity of the comparator arms used in the different trials. Bolton and colleagues performed a placebo-controlled trial, while Carvalho and colleagues used a morphine-based control treatment[15]. Udelsman and colleagues compared methadone to

Table 1 Summary of included studies

Study	Participants (treatment/control)	Study type	Cardiac procedure(s)	Relevant exclusion	Treatment dose	Control	Ongoing pain management	Outcome
Randomized controlled trials								
Murphy et al. (2015) [8]	156 (note 8 excluded after enrollment) (77/79)	RCT comparing methadone to fentanyl	CABG, valve surgery or combined CABG/valve, ASD repair	Preoperative renal failure Hepatic dysfunction LVEF <30% Preoperative inotrope or IABP requirement Emergency status History opioid abuse	Methadone 0.3 mg/kg (maximum dose 30 mg)	12 mcg/kg fentanyl (maximum dose 1200 mcg)	ICU: 2 mg morphine bolus with >mild pain Ward: 10 mg hydrocodone, paracetamol 325 to 650 mg	No difference in time to wean off ventilatory support OR to extubation. Methadone group had: - Decreased morphine requirement 1st 24 h (6 mg versus 10 mg) - Improved pain scores at 12 h after extubation - Less total morphine use in 1st 72 h (8 to 14 mg) - Lower pain scores at rest and with coughing within 1st 72 h No difference in opioid-related side-effects
Bolton et al. (2019) [15]	21 (9/12)	RCT	Isolated CABG	Concomitant valve Preoperative renal failure Hepatic dysfunction LVEF <30% QTc >440 ms (men), 450 ms (women) Preoperative inotrope or IABP requirement Emergency surgery Preoperative opioid use Known opioid abuse	Methadone syrup at 0.3 mg/kg (maximum 30 mg)	Placebo	ICU: morphine (2–5 mg) IV every 5 min until extubation. Post-extubation 0.05mg/kg morphine every 10 min (nurse-controlled) Ward: PCA 0.015 mg/kg morphine with 6-min lock-out Paracetamol 650 mg Q6rhly	Slight difference with 2 patients in placebo arm history chronic pain. No difference in postoperative pain scores. Methadone reduced morphine requirement first 24 h by mean 23 mg (95% CI 37–13 mg, $P<0.005$). No difference beyond 24 h. No difference in opioid-related side-effects.

Table 1 (continued)

Study	Participants (treatment/control)	Study type	Cardiac procedure(s)	Relevant exclusion	Treatment dose	Control	Ongoing pain management	Outcome
Carvalho et al. (2017) [12]	104 (52/52)	RCT Double-blind, comparing methadone to morphine	Isolated off-pump CABG	Illicit drug use Allergy to any medication Intubation >12 h postoperatively (expected)	Intravenous methadone at conclusion anesthesia. Dose 0.1 mg/kg, corrected weight	Intravenous morphine at conclusion anesthesia. Dose 0.1 mg/kg, corrected weight	ICU: IV dipyrone 1g 6 hourly, morphine (0.03 mg/kg, max 0.1 mg/kg within 4 h).	Methadone group had: - Lower postoperative pain scores at 24 h, but not 36 h - Lower morphine use - Shorter time to first analgesic Reported satisfactory analgesic effect at 36 h (pain score ≤3) with methadone reported as 22% more efficacious with a number needed to treat of 6 patients.
Udelsmann et al. (2011) [14]	55 (18/19/18)	RCT with three groups: methadone, morphine and control	Cardiac surgery with cardiopulmonary bypass	Illicit drugs or antidepressants Psychiatric diseases Allergy to any of the drugs Planned intubation >24 h	Intravenous methadone, dose 20 mg	Control include: 20 mg of morphine, 2 mL of saline	ICU: 0.03 mg/kg morphine as required administered by ICU nursing staff	No difference in time of anesthesia or until extubation The methadone group had: - Longer time to first analgesic - Significantly lower analgesic requirement - Significantly better quality of analgesia within the first 24 h - - Lower incidence of nausea and vomiting

Table 1 (continued)

Study	Participants (treatment/ control)	Study type	Cardiac procedure(s)	Relevant exclusion	Treatment dose	Control	Ongoing pain management	Outcome
Murphy et al. (2020) [16]	Cardiac arm of trial had 156 patients, with response from: - 1 month: 104 - 3 months 100 - 6 months: 83 - 12 months: 65	Follow-up of two RCTs (one spinal surgery, one cardiac surgery)	CABG, valve surgery or combined CABG/ valve, ASD repair	Preoperative renal failure Hepatic dysfunction LVEF <30% Preoperative inotrope or IABP requirement Emergency status History opioid abuse	Intravenous methadone (0.3 mg/kg) before cardiopulmonary bypass	12µg/kg fentanyl before cardiopulmonary bypass	ICU: 2mg morphine bolus with >mild pain Ward: 10mg hydrocodone, paracetamol 325mg to 650mg	No difference in observed responses between intervention and control Lower postoperative pain at 1 month with methadone, and then no difference (low for both cohorts) No difference in requirement for opioid medications low in both groups, although statistically lower in methadone group at 3 months
Observational studies								
Eisenbraun et al. (2023) [17]	4326 patients Opioid (control) 2307 patients Multimodal 1 1244 patients Multimodal 2 (methadone) 775 patients	Single-center retrospective	Adult cardiac surgical patients via sternotomy with cardiopulmonary bypass	Requirement for mechanical circulatory support Transplantation History congenital heart anomalies Emergent procedures Regional anesthesia	Note there were three regimes used. In the methadone group ("multimodal 2"), given 0.3 mg/kg (max 30 mg) on induction Also dexmedtomidine, paracetamol and ketorolac All groups used fentanyl	Multimodal 1: - Ketamine 50 mg with induction - Ketorolac - Paracetamol Control ("opioid" group): - Induction as per provider	Postoperative care differed between groups: (2) (1) "Control": Traditional with PCA until chest tubes out and then oxycodone + paracetamol (4) (3) Multimodal 1 Paracetamol PR + morphine 15–30 mg PR in ICU with ketamine or oxycodone for PRN (6) (5) Multimodal Paracetamol orally + ketorolac IV with oxycodone and hydromorphone for breakthrough	Methadone group had: - Lowest opioid requirement POD 1 - Lowest median OME by discharge (0mg vs 5mg multimodal group 1, 7.5mg opioid group) - Lowest pain scores first 72 h

Table 1 (continued)

Study	Participants (treatment/control)	Study type	Cardiac procedure(s)	Relevant exclusion	Treatment dose	Control	Ongoing pain management	Outcome
Wang et al. (2021) [13]	117 patients (52/65)	Single-center retrospective	CABG, valve, or combine CABG/valve	Off-pump surgery Intubated >24 h	Intravenous methadone, with dose varying depending on clinician (0.1 to 0.4 mg/kg—86% doses within 0.15 to 0.25 mg/kg)	"Usual care" including intravenous fentanyl, hydromorphone or morphine	Not clearly defined, but additional analgesia included paracetamol, ketorolac and additional opioids as required (measured as MME)	Methadone cohort received: - Significantly less additional intraoperative opioids (MME) - 44% reduction in MME on POD 0 No difference in pain scores between two groups No difference in time to extubation or ICU length of stay

Table 2 Risk of bias assessment for the included RCTs according to the Cochrane RoB 2 matrix

Authors	Risk of bias domains					Global assessment
	Randomization	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reporting	
Murphy et al. (2015) [8]	Low	Low	Low	Low	Low	Low
Bolton et al. (2019)	Low	Some concerns	Some concerns	Low	Low	Some concerns
Carvalho et al. (2017) [12]	Some concerns	Low	Low	Low	Low	Some concerns
Udelsmann et al. (2011) [14]	Some concerns	Low	Low	Some concerns	Low	Some concerns
Murphy et al. (2020) [16]	Low	Low	Some concerns	Low	Low	Some concerns

both placebo and morphine controls [14]. As such, two separate meta-analyses were performed for the performance of methadone compared to that of placebo and that of morphine. Neither the original RCT performed by Murphy and colleagues nor the extension of this trial were included in the meta-analyses, as these authors randomized patients to the addition of either methadone or fentanyl. As no other included RCTs used fentanyl as a comparator, meta-analysis was not possible. Figures 2 and 3 depict the standardized effect sizes of the included RCTs via Cohen's *d* statistic, in addition to the random effects pooled effect size. Pooled analysis did not suggest a statistically significant difference between methadone and placebo or between methadone and morphine with respect to standardized effects on postoperative pain scores at 24 h after surgery.

Wang et al. published a single-center, retrospective study that investigated intravenous methadone administered intraoperatively (the dose varied among clinicians from 0.1 to 0.4 mg/kg, with 86% of doses ranging from 0.15 to 0.25mg/kg) to "usual care" (fentanyl, hydromorphone, or morphine) [13]. They found no difference in postoperative pain scores within 24 h of surgery (3.2 vs 3.1, p=0.422).

Eisenbraun et al. published a single-center, retrospective study of 4326 patients [17]. The patients were divided into three cohorts. The first was the standard of care, which was opioid-based with induction as per the provider. The second group was multimodal with ketamine and ketorolac on induction in addition to fentanyl [17]. The final group received intravenous methadone on induction (0.3 mg/kg, maximum dose 30 mg), dexmedetomidine and ketorolac in addition to fentanyl[17]. There were also differences in postoperative pain management (Table 1) [17]. This study revealed that patients treated with methadone for the first 72 h had lower pain scores according to the NPRS than according to the standard of care [17]. The methadone cohort also had lower pain scores according to the NPRS than did the ketamine cohort for the first 12 h, with no difference after that [17].

Postoperative opioid requirements prior to discharge

All four randomized controlled trials evaluated the effect of methadone on postoperative opioid requirements in the form of morphine. The intravenous administration of morphine was either nurse-administered or patient-controlled (PCA). Three of the four studies reported lower morphine requirements in the immediate postoperative period.

Murphy et al. reported lower morphine requirements in the first 24 h (6 mg vs 10 mg, p<0.001), although this difference did not persist at 48 or 72 h [8]. Furthermore, fewer patients required ≥20 mg of morphine within the first 24 h (2.6% vs 29.1%, p<0.001) [8]. There was no difference in the use of oral pain relief tablets for the first 72 h [8].

Bolton et al. also demonstrated lower postoperative morphine requirements via PCA at 24 h (mean reduction 23 mg, p<0.005) and in nurse-controlled patients (11.2 mg vs. 20 mg, p=0.007) [13] There was no difference beyond this. Carvelho et al. reported a lower percentage of patients who used morphine during the postoperative period, but the difference was not quantified [12].

Udelsmann et al. reported lower analgesic requirements in the first 24 h than in both the morphine and control groups but did not observe a specific reduction in the requirement between the methadone and morphine groups [14].

Both retrospective cohort studies reported postoperative opioid requirements[13, 17]. Wang et al. reported a 44% reduction in postoperative opioid requirements measured as the morphine milligram equivalent (MME) on postoperative day 0 (15.8 vs 36, p=0.025) but not on postoperative day 1 [13].

Table 3 Risk of bias assessment for the included observational studies according to the ROBINS-I matrix

Authors	Risk of bias domains							Global assessment
	Confounding	Selection	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of reporting	
Eisenbraun et al. (2023) [17]	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Wang et al. (2021) [13]	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate

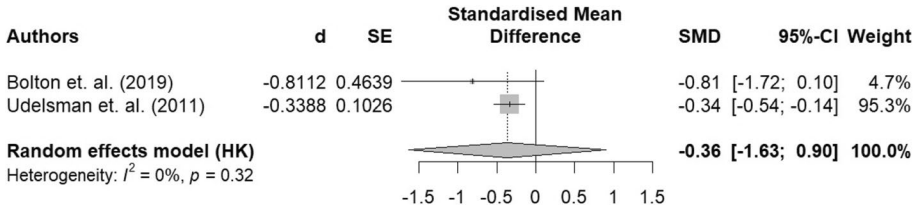

Fig. 2 Random effects model pooled analysis of the standardized mean difference in postoperative pain scores at 24 h for patients receiving methadone versus those receiving morphine. Negative scores indicate favorable pain control with methadone

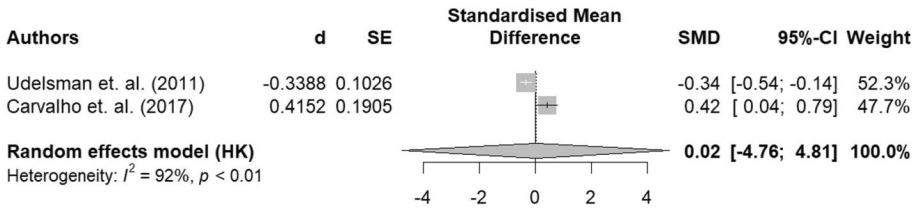

Fig. 3 Random effects model pooled analysis of the standardized mean difference in postoperative pain scores at 24 h for patients receiving methadone versus those receiving morphine. Negative scores indicate favorable pain control with methadone

Eisenbraun et al. demonstrated lower postoperative opioid requirements on postoperative days 0, 1, 2, and 3 compared with both the standard of care (i.e., opioid-based induction) and the alternative ketamine-based multimodal regime [17]. On postoperative day 0, there was an 82% reduction in opioid requirements compared to the standard of care and a 64% reduction compared to the ketamine-based cohort [17].

Opioid requirements at discharge

There was no comment on opioid requirements at discharge in any of the four randomized controlled trials. The extended follow-up study by Murphy et al. from the original randomized controlled trial examined opioid requirements at 1, 3, 6, and 12 months[16]. Eisenbraun et al. was the only retrospective study to report on oral morphine equivalent (OME) requirements at discharge [17]. The authors found a lower OME at discharge in the methadone group than in the standard opioid-based group (0 mg vs 7.5 mg, p<0.001) and in the multimodal ketamine-based cohort (0 mg vs 5 mg, p<0.001) [17].

Long-term follow-up

The extended follow-up study from their initial randomized controlled trial by Murphy et al. was the only study to report outcomes beyond discharge [16]. The authors evaluated patients at 1 month (67% of the initial cohort), 3 months (64% of the initial cohort), 6 months (53% of the initial cohort), and 12 months (42% of the initial cohort) [16]. At 1 month, there was a lower frequency of postsurgical pain at 1 month (median once per week vs twice per week, p=0.004), with no difference beyond this [16]. There was no difference in analgesic requirement between the two cohorts at any time point [16].

Adverse effects

All four RCTs reported on the incidence of adverse effects to some degree. Murphy et al. showed no difference in the rates of nausea, vomiting, pruritus, hypoxia, sedation, respiratory complications, cardiac complications, renal complications, neurological complications, or infection complications between methadone and fentanyl

cohorts in the first 72 h [8]. There was no difference in the median ICU length of stay (30.5 h vs 47 h, p=0.452) or median hospitalization duration (7 days, p=0.515) [8].

Udelsmann et al. reported a significantly lower incidence of nausea and vomiting in patients treated with methadone than in those treated with morphine or placebo (1 vs 6 vs 9, p=0.013) [14]. Carvelho et al. reported no difference in the incidence of adverse effects, nausea, vomiting, or respiratory failure[12]. Bolton et al. also found no difference in the incidence of nausea, vomiting, pruritus, constipation, or hypoxia after 72 h compared to placebo [15].

Both retrospective studies evaluated multiple end points. Wang et al. found no difference in the time to extubation (median 3.8 h vs 3.9 h, p=0.271), ICU length of stay (39.7 h vs 42 h, P=0.940), or requirement for non-invasive ventilation (7.7% vs 6.2%, p>0.999) [13]. Eisenbraun et al. showed comparable rates of nausea and vomiting with methadone compared to standard of care with opioids [17]. However, there was a 53% reduction in nausea and vomiting in the multimodal ketamine-based group compared to either opioid group [17].

Discussion

Pain management in cardiac surgical patients is an important and highly topical concern. There is emerging evidence of the negative impact of opioids both immediately and long-term after surgery, with increased long-term mortality and morbidity and increased healthcare costs being associated with new opioid dependence [18–21]. Santosa et al. examined mortality and morbidity within 12 months in a 20% sample of Medicare beneficiaries who underwent a surgical procedure over a 10-year period [18]. A total of 3% (6874 patients) of this cohort of 229,898 patients went on to develop a persistent opioid requirement [18]. Patients who developed a new persistent opioid requirement were significantly more likely to die within 12 months of their procedure (hazard ratio 3.44, 95% CI 2.99–3.96) [18]. They were also more likely to have a serious fall or fall-related injury or present to the emergency department [18]. There has been an increasing push to adopt a more multimodal approach to improve perioperative outcomes and reduce opioid dosing. This is an important pursuit, as the long-term adverse effects of opioid use are well documented [18–21].

A study published by Song et al. in 2022 investigated the effects of chronic opioid use in patients with non-cancer pain [22]. The authors found that over a 10-year period (2010–2019), the prevalence of chronic opioid use increased from 0.46% in 2010 to 2.63% in 2019 [22]. Patients with chronic opioid use had a greater 10-year all-cause mortality, with a hazard ratio of 1.21 (95% CI 1.13–1.31, p<0.01) [22]. Long-term opioid use is also associated with substantial morbidity, including hyperalgesia, tolerance, and withdrawal [23]. Despite these risks of chronic opioid use, inadequate pain relief post-sternotomy for cardiac surgery is associated with adverse outcomes in the short and long term [23]. Chronic pain following sternotomy is not infrequent, and therefore, despite concerns about chronic opioid use, patients require adequate analgesia to prevent immediate and long-term complications. With the development of multimodal analgesia, opioid-sparing regimens are important for reducing overall opioid consumption during the perioperative period [2].

This systematic review suggested that using methadone either preoperatively or intraoperatively may not only lessen immediate postoperative pain scores but also reduce opioid requirements at discharge. This may have an important effect on reducing chronic pain and opioid dependence in patients undergoing sternotomy for cardiac surgery. However, we could only find one study that attempted to evaluate the impact of intraoperative methadone on medium- to longer-term outcomes, making the extrapolation of the impact of perioperative methadone on chronic pain and chronic opioid dependence challenging [16]. In addition, another retrospective study showed a significantly reduced oral morphine equivalent (OME) at discharge in a cohort treated with preoperative methadone [17]. Higher OME at discharge is associated with an increased likelihood of opioid dependence, which is a risk factor for chronic pain and morbidity [24]. Furthermore, greater acute postoperative pain has been associated with the development of chronic pain and opioid dependency [25]. It could be hoped that the addition of methadone in the pre- or intraoperative setting will translate to reduced chronic pain and opioid dependence by reducing immediate postoperative pain and opioid requirements and by reducing the need for opioids at discharge. However, further research is needed to determine whether pre- or intraoperative methadone administration can lead to reduced chronic pain and opioid dependence.

Methadone, though, is an attractive addition to the armament in pain management because of its potent analgesic effects, which are long-lasting and have additional effects on the NDMA receptor [7]. It has been shown to be effective at reducing postoperative opioid requirements and postoperative pain scores and improving patient satisfaction with pain management in patients undergoing major spinal surgery, gynecological surgery and general surgery [26].

This systematic review has multiple limitations. First, the quality of a systematic review is dependent on the studies included within it. Of the included RCTs, all excluding Murphy et al. raised some concerns about

at least one domain of risk of bias assessment [16]. Principally, these issues are related to poor reporting of the precise methods employed for randomization or imperfect randomization sequences. In the case of two studies, concerns were raised regarding missing data or poor protocol adherence, leading to patients who were originally randomized to a treatment group being excluded from the analysis. The two observational studies are limited by the inherent bias of their study design. Although the study by Eisenbraun et al. was large (over 4000 patients), there was significant variation not only in the preoperative/intraoperative intervention but also in the postoperative analgesia regime [17]. This makes it challenging to determine the exact effect of preoperative methadone on postoperative opioid requirements and pain scores.

Second, the studies included were all relatively small cohorts (with the exception of the retrospective study by Eisenbraun et al.) [17] This impacted the ability to combine the results for meta-analysis. Third, there was also variation in the postoperative analgesia regime, which makes the generalizability of the effect of preoperative/intraoperative methadone challenging.

Finally, all studies examined immediate postoperative outcomes (with the exception of the longer-term follow-up study by Murphy et al.) [16]. The effect of methadone preoperatively/intraoperatively on longer-term opioid use and chronic pain scores is important given the known high rates of chronic pain and opioid dependence post sternotomy [3, 27].

This systematic review provides the scope for future research. There is clearly a need to improve the perioperative pain management of patients undergoing sternotomy to limit the development of chronic pain and reduce the incidence of new opioid dependence. Opioid stewardship is important, and all efforts should be made to explore and develop new techniques to lessen the development of long-term opioid dependence.

Conclusions

Methadone may represent a valuable addition to the armamentarium in patients undergoing sternotomy for cardiac surgery. The findings of the existing publications on this subject are variable; some authors have reported benefits in reducing postoperative pain scores and the need for opioids perioperatively, while others have not observed these benefits. Further investigation in the form of randomized trials is needed .

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Authors' contributions
Both authors (JG and LC) were involved in the conception and study design. Both authors reviewed the available manuscripts and determined the most appropriate studies to include. Author JG then wrote the manuscript, which was reviewed by author LC. Senior authors JE, JR, and WP were involved in adjudication with articles for inclusions/exclusion and all reviewed and edited the manuscript as appropriate.

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Availability of data and materials
The data available with a summary of the included studies is provided in Table 1.

Declarations

Ethics approval and consent to participate
As this was a review of the available literature, ethics approval was not applicable.

Consent for publication
This was not applicable.

Competing interests
The authors declare that they have no competing interests.

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