Review Article

Intrathecal Morphine for Cardiac Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Cardiac surgeries often result in significant postoperative pain, leading to considerable use of opioids for pain management. However, excessive opioid use can lead to undesirable side effects and chronic opioid use. This systematic review and meta-analysis aimed to evaluate whether preoperative intrathecal morphine could reduce postoperative opioid consumption in patients undergoing cardiac surgery requiring sternotomy. We conducted a systematic search of Cochrane, EMBASE, and MEDLINE databases from inception to May 2022 for randomized controlled trials that evaluated the use of intrathecal morphine in patients undergoing cardiac surgery. Studies that evaluated intrathecal administration of other opioids or combinations of medications were excluded. The primary outcome was postoperative morphine consumption at 24 h. Secondary outcomes included time to extubation and hospital length of stay. The final analysis included ten randomized controlled trials, with a total of 402 patients. The results showed that postoperative morphine consumption at 24 h was significantly lower in the intervention group (standardized mean difference -1.43 [-2.12, -0.74], 95% CI, $P < 0.0001$). There were no significant differences in time to extubation and hospital length of stay. Our meta-analysis concluded that preoperative intrathecal morphine is associated with lower postoperative morphine consumption at 24 h following cardiac surgeries, without prolonging the time to extubation. The use of preoperative intrathecal morphine can be considered part of a multimodal analgesic and opioid-sparing strategy in patients undergoing cardiac surgery.

Keywords: Cardiac surgery, Intrathecal morphine, Meta-analysis, Opioid, Pre-emptive analgesia, Spinal anesthesia

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INTRODUCTION

Cardiac surgeries are among the most commonly performed major surgical operations.[1-3] Between 2008 and 2017, over 2.5 million cardiac surgeries were carried out in the United States.[4] The most common approach is via median sternotomy,[5] providing good exposure but also giving rise to significant postoperative pain with nociceptive, neuropathic, and referred components.[6-8] Poor postoperative pain control affects adequate coughing, deep breathing, and mobilization and is associated with increased morbidity, disability, and reduced quality of life. It may also lead to chronic postoperative pain, prolonged opioid use during and after hospitalization, and increased cost of care.[9-11]

Pain management protocols vary widely among institutions and may involve different medication classes and routes of administration.[12,13] Systemic drug use may be limited due to their side effect profile, with systemic opioids

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being associated with significant adverse effects such as respiratory depression, constipation, pruritus, nausea, and vomiting.[14] Pre-emptive analgesia, the administration of a drug before the painful stimulus occurs, may reduce postoperative pain and the need for administering postoperative analgesics.[15,16]

Due to the multifactorial nature of the pain stimulus involved in cardiac surgeries, a multimodal approach to analgesia is biologically plausible and may lead to improved outcomes.[6,17] Preoperative intrathecal opioids can potentially play an essential role in this approach. Morphine, one of the most commonly used intrathecal opioids,[18] acts primarily as a μ-opioid receptor agonist, binding to mu receptors in the spinal cord. Intrathecal morphine has been widely studied in cardiac surgery. However, due to the small sample size of previous randomized controlled trials, its role remains somewhat uncertain. Therefore, we performed a systematic review and meta-analysis of studies comparing the injection of intrathecal morphine with a placebo in patients undergoing cardiac surgery via median sternotomy.

METHODS

Eligibility criteria and search strategy

We conducted a systematic review of the literature from the inception of intrathecal morphine[1980] to May 2022, using three databases: Medline, Embase, and Cochrane Library. Randomized controlled trials evaluating the use of intrathecal morphine in patients undergoing cardiac surgery via median sternotomy were included. We excluded studies with pediatric patients (less than 18 years old) that performed minimally invasive cardiac surgery; administered intrathecal opioids other than morphine; written in a non-English language; and with overlapping patient populations. The systematic review and meta-analysis were performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[19]

Search terms included invasive cardiac surgery, cardiac surgery, coronary artery bypass grafting (CABG), heart surgery, intrathecal morphine, subarachnoid morphine, intraspinal injection, intrathecal opioids, and intrathecal narcotic. The search strategy is outlined in Figure 1.

This meta-analysis was registered on Prospero in June 2022 under the inscription CRD42022340074.[20] Morphine consumption at 24 h was chosen as the primary outcome. Secondary outcomes included hospital length of stay (LOS) and time to extubation.

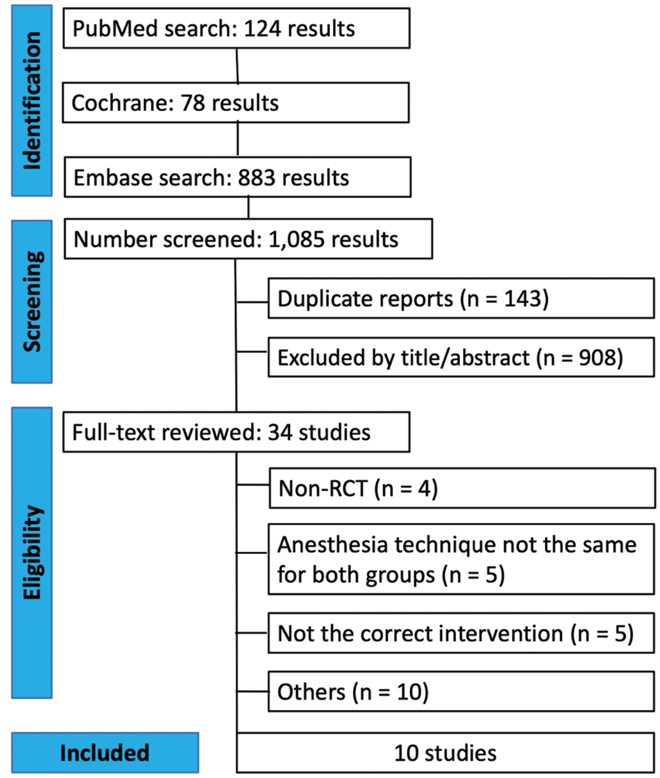

Figure 1: PRISMA diagram

Data analysis and quality assessment

A random effects model was used for the outcomes of interest. Two authors independently extracted baseline characteristics [Table 1] and outcomes data using prespecified criteria for the search, data extraction, and quality assessment. Disagreements were resolved by consensus among the three authors. Weighted and standardized mean differences were used to pool continuous outcomes with a 95% confidence interval. Heterogeneity was evaluated with the Cochran Q test and I2 statistics; *P* values inferior to 0.10 and I^2 >25% were considered significant for heterogeneity. DerSimonian and Laird's random effects model was used in pooled outcomes with high heterogeneity. Review Manager 5·4.1 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis.

The Cochrane Collaboration tool was used for quality assessment/risk of bias of individual randomized studies. Each trial received a high, low, or unclear risk of bias score in five domains: selection, performance, detection, attrition, and reporting biases [Table 2].

Role of funding

There was no funding source for this study. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit it for publication.

Table 1: Study and Population Characteristics

Study	Design	Number of Patients ITM/GAA	Male, % ITM/GAA	Weight (kg), ITM/GAA	Age* ITM/GAA	Mean CPB time, min ITM/GAA	Intra-operative Sedatives Used
Alhashemi, 2000[46]	RCT	31/19	80/89	89.2/90.5	60.6/64.4	72.3/81.8	Fentanyl, midazolam
Boulanger, 2002[21]	RCT	20/22	75/81	NA	56.8/53.4	43.7/47.5	Sufentanyl, midazolam, propofol
Casey, 1987[47]	RCT	19/21	84/90	81/75	56/59	93/95	Fentanyl, Diazepam
Chaney, 1996[24]	RCT	30/30	63/60	76/82	65/64	110.2/113	Fentanyl, Midazolam, Isoflurane
Chaney, 1997[30]	RCT	19/21	68/76	85/83	64/61	116/120.4	Fentanyl, Midazolam, Isoflurane
Elgendy, 2017[44]	RCT	22/22	50/45	56/64.4	26.5/25.9	99.8/98.3	Fentanyl, propofol, Isoflurane
Jacobsohn, 2005[43]	RCT	22/21	81/90	82/81	62/64	72/54	Sufentanyl, Midazolam, Isoflurane
Roediger, 2006[25]	RCT	15/15	100/100	85/82.5	65.5/60.7	91/83	remifentanil, Propofol
Vanstrum, 1988[45]	RCT	16/14	93/78	83/74	63/66	NA	Sufentanil, diazepam, Isoflurane
Yapici, 2008[42]	RCT	12/11	75/63	72.8/62.1	55,3/59,2	133/120	Remifentanil, ethomidate, sevoflurane

*Mean or median; ITM: Intrathecal morphine; NA: not available; RCT: randomized controlled trial; GAA: General anesthesia alone; CPB: cardiopulmonary bypass; Kg: kilogram

Table 2: Risk of Bias Domains

Study	D1	D2	D3	D4	D5	Overall
Alhashemi 2000[46]	+	+	+	-	+	+
Boulanger 2007[21]	+	+	+	-	-	-
Casey 1987[47]	+	+	-	+	+	+
Chaney 1996[24]	+	-	-	-	+	-
Chaney 1997[30]	+	-	-	+	+	-
Elgendy 2008[44]	+	+	+	-	-	-
Jacobson 2005[43]	+	+	+	+	+	+
Roediger 2006[25]	+	+	+	+	+	+
Vanstrum 1988[45]	+	+	-	+	+	+
Yapici 2008[42]	+	+	+	-	+	+

Domains: D1: Bias arising from randomization process, D2: Bias due to deviations from intended intervention, D3: Bias due to missing outcome data, D4: Bias in measurement of the outcome, D5: Bias in selection of the reported result. Judgment: +: Low concern, -: Some concerns

RESULTS

A total of 1,085 articles were screened through Medline, Cochrane, and Embase databases [Figure 1]. Of these, 1,051 were excluded based on predetermined criteria, and 34 were read in full. Ten randomized controlled trials were included in the meta-analysis, all of which used the same anesthetic technique for both intervention and control groups. The sum of patients from all studies was 402, with 206 patients in the intervention group and 196 in the control group. The median age ranged from 26.5 to 65.5 years in the intervention group and from 25.9 to 66 years in the control group [Table 1]. Boulanger 2002 had an extra intervention group that received subcutaneous morphine[21]; this subcutaneous group was excluded from the meta-analysis.

Five studies evaluated morphine consumption 24 h after surgery, (Alhashemi 2000[46], Boulanger 2002[21], Casey 1987[47], Chaney 1997[30], Vanstrum 1988[45]) with no study having a minimum predetermined time between the intrathecal morphine injection and the first morphine dose for postoperative pain control. Mean morphine consumption was significantly lower in the intervention group (-1.43 [-2.12, -0.74], 95% CI, $P < 0.0001$) as shown in Figure 2.

In six studies, (Boulanger 2002[21], Chaney 1996[24], Chaney 1997[30], Elgendy 2017[44], Jacobsohn 2005[43], Roedinger 2006[25]) the mean hospital length of stay varied from 5.3 to 9.8 days in the intervention group and from 5.8 to 10.7 days in the control group. No significant difference was observed for this outcome between the two groups (-0.19 [-0.43, 0.06], 95% CI, $P = 0.14$), as demonstrated in Figure 3.

Nine studies reported mean time to extubation, (Alhashemi 2000[46], Boulanger 2002[21], Casey 1987[47], Chaney 1996[24], Chaney 1997[30], Elgendy 2017[44], Jacobsohn 2005[43], Roedinger 2006[25], Yapici 2008[42]) which ranged from 41.4 to 1,308 minutes in the intervention group and from 39.2 to 1,314 minutes in the control group. No significant difference was found between the two groups (0.03 [-0.24, 0.31], 95% CI, $P = 0.81$), as shown in Figure 4.

DISCUSSION

Opioids are extensively used for managing postoperative pain. Despite their analgesic properties, systemic use might lead to undesirable effects as well as an increased likelihood of opioid use disorder.[17,22] Preoperative intrathecal morphine has been hypothesized to reduce postoperative opioid consumption. Our meta-analysis findings have corroborated this hypothesis.

This finding has important implications. Patients who receive preoperative intrathecal morphine may have better pain control and are therefore exposed to less systemic opioids compared to patients who do not undergo the intervention. This is potentially impactful as enhanced pain management might have consequences well beyond just better patient comfort. Nociceptive stimuli prevent effective coughing and deep breathing, resulting in an increased risk of respiratory complications, such as atelectasis and pneumonia.[23] Brown *et al.* reported that out of 35,817 opioid-naive patients who underwent CABG or valve replacements, 3,430 patients (9.6%) had a new persistent opioid use within 90 to 180 days.[17] This is significant and carries several potentially harmful long-term consequences associated with chronic opioid use. Therefore, preoperative intrathecal morphine administration might be one strategy to reduce postoperative pain and the risk of chronic opioid misuse.

Our meta-analysis has demonstrated a significant reduction in morphine consumption within the first 24 h post-surgery in the intervention group. However, whether this effect is sustained over a longer period remains uncertain. Notably, one study included in this meta-analysis reported morphine consumption at 72 h post-surgery, and another reported consumption at 48 h and 72 h. Chaney *et al.* reported a reduction in postoperative morphine consumption at 48 h in the intervention group but observed no significant difference between groups from 48 to 72 h.[24] Roediger and colleagues reported similar findings, although the cumulative consumption over a 72-h period significantly favored the intervention group.[25] Originally, our study design encompassed evaluations of opioid consumption at 24, 72, and 120 h after surgery. However, as meta-analyses are confined to outcomes reported in previous trials, we had to restrict our reporting to morphine consumption solely 24 h after surgery.

Cardiac disorders and procedures rank among the most costly conditions treated in United States hospitals, and there is a noteworthy interest in cost-containment efforts.[26-28] Shortening hospital length of stay (LOS) is a commonly employed strategy to decrease medical expenses. In our systematic review, three studies provided statistically significant evidence of reduced LOS. However, our meta-analysis did not identify a significant reduction in LOS.

Despite Fitzpatrick *et al.* reported shorter time to extubation for patients receiving preoperative intrathecal morphine compared to no intrathecal drug,[29] the use of systemic opioids could be associated with respiratory depression and a potential delay in extubation time. As all the studies included in this meta-analysis had a protocol for extubation outside the operating room, we analyzed the impact of intrathecal morphine on time to extubation by grouping the studies. Among three studies analyzed (Boulanger 2002, Chaney 1996, Chaney 1997),[21,24,30] a total of nine cases of delayed extubation were reported, with eight cases occurring in the intrathecal morphine group and one case in the placebo group. Despite that, statistical analysis did not demonstrate a significant difference in time to extubation between intervention and control groups. It is worth noting that Chaney 1996[24](n = 60) administered a higher dose of morphine intrathecally (4 mg) and had only one patient with delayed extubation, whereas Boulanger[21] 2002 (n = 37) used a smaller amount of morphine for neuraxial analgesia (0.02 mg/kg to 1 mg), but had five patients with delayed extubation (four in intrathecal morphine group and one control group). Therefore, we did not observe an increase in the number of delayed extubation events with a higher dose of intrathecal morphine.

Zangrillo *et al.* conducted a meta-analysis in 2009 comparing the use of spinal analgesia to non-spinal analgesia in cardiac surgeries.[31] In their meta-analysis, they included studies that used mixed opioids, bupivacaine, and clonidine intrathecally. They found no significant difference between placebo and control groups in terms of mortality and length of hospital stay but reported a higher incidence of postoperative pruritus in the spinal anesthesia group. Our meta-analysis yielded a similar result for the length of hospital stay but only included studies using intrathecal morphine alone. By limiting confounding factors, such as the use of opioid mixtures, clonidine, or local anesthetics, we aimed to isolate the effect of morphine and reduce potential biases. In contrast, Liu *et al.* conducted a meta-analysis in 2004 that included various intrathecal analgesics and reported a modest reduction in systemic morphine use and global pain scores, but also found an increased incidence of pruritus.[32]

Despite the numerous advantages of spinal anesthesia, this technique may have certain drawbacks, including the potential for serious complications. Intrathecal morphine has the potential for delayed respiratory depression. Studies indicate an incidence of respiratory depression ranging from 0.01% to 7% following neuraxial opioid use.[33,34] Therefore, The American Society of Anesthesiology recommends enhanced monitoring for patients receiving both neuraxial opioids and parenteral opioids, sedatives, hypnotics, or magnesium.[33] Another complication, although rare, is spinal hematoma formation. The consequences of spinal hematoma can be significant, resulting in irreversible neurological damage in some cases.[35] A cohort study conducted by Bodilsen *et al*. reported an incidence of spinal hematoma of 0.20% in patients without coagulopathy and 0.23% in patients with coagulopathy.[36] In cardiac surgeries, which often involve heparinization for cardiopulmonary bypass, the risk of this complication might be higher. However, there were no reported cases of spinal hematoma or neuraxial hematoma in the studies included in our meta-analysis.

One risk factor for spinal hematoma is a traumatic spinal tap.[37] None of the studies in our meta-analysis reported a

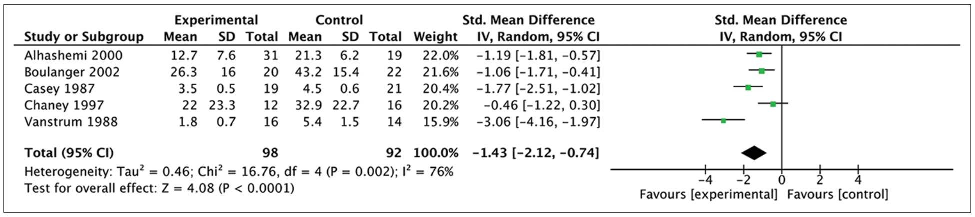

Figure 2: Morphine consumption at 24 hours

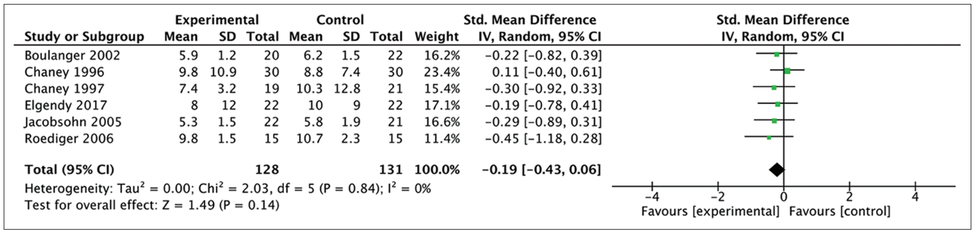

Figure 3: Length of hospital stay

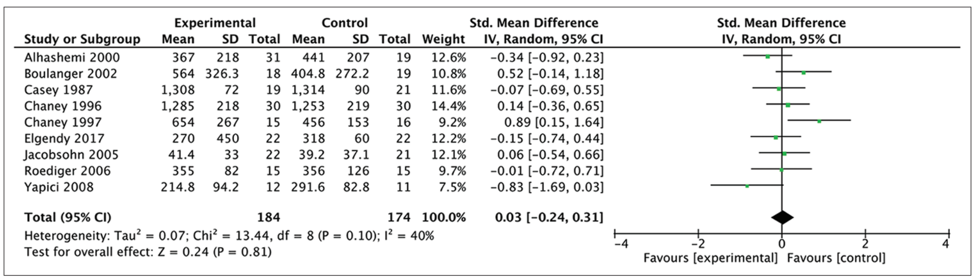

Figure 4: Time to extubation

traumatic tap. To prevent spinal hematoma, the American Society of Regional Anesthesia and Pain Medicine (ASRA) published a newsletter recommending heparinization after 60 minutes of neuraxial analgesia and delaying surgery for 24 h in case of a bloody tap.[38] Physicians should consider this recommendation when administering intrathecal morphine before surgeries with heparinization and cardiopulmonary bypass.

Our meta-analysis sheds new light on the management of postoperative pain in patients undergoing cardiac surgery. Currently, most hospitals use a combination of systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and anti-convulsants (e.g., gabapentin) for pain control.[39,40] However, in many instances, they do not include regional or neuraxial analgesia. Our findings suggest that preoperative administration of intrathecal morphine can potentially be incorporated into a multimodal pain control regimen for patients undergoing cardiac surgery. Furthermore, it can be considered as an option for opioid-sparing surgery. Dhawan *et al.* conducted a randomized controlled trial on intrathecal morphine for minimally invasive cardiac surgeries and observed a reduction not only in postoperative opioid consumption but also in pain scores.[41] Given the opioid crisis, it is crucial to consider opioid-sparing techniques when developing an anesthetic plan for patients.

Our study has many limitations. Despite the inclusion of several randomized controlled trials, our final sample size of 402 patients is still relatively small, limiting power as well as generalizability. We found considerable heterogeneity in two of our outcomes (morphine consumption at 24 h and time to extubation), which limits validity. We hypothesized that heterogeneity occurred most likely due to variations in intraoperative and postoperative protocols used in different hospitals. For example, postoperative morphine consumption may have varied depending on the choice of intraoperative opioid, or the use of additional non-opioid medications for postoperative pain management. However, although protocols varied in different hospitals, a given hospital's intervention and control groups were under the same management strategy. Another important limitation has to do with morphine being the only opioid included in the outcome of our studies. Currently, postoperative pain is managed with different types of opioids, not only morphine. The fact that the studies included in this meta-analysis did not report their results in morphine equivalents limits our generalizability. Furthermore, due to the lack of data on pain scores, the reduction in postoperative morphine consumption cannot confirm a concomitant reduction in postoperative pain. Four articles (Yapici 2008; Jacobsohn 2005; Elgendy 2017; Roediger 2006) showed a significant reduction in pain scores in the intervention group,[25,42-44] whereas two (Boulanger 2002; Vanstrum 1988) did not find a statistically significant reduction in pain scores.[21,45] Most studies presented their data on continuous graphs; therefore, to perform the analysis of pain scores, we contacted the corresponding authors and asked for the raw data. Due to the low number of responses (two), a statistical analysis was not feasible.

Ours is the first meta-analysis that compares the use of preoperative intrathecal morphine to a placebo. Our study aimed to explore how this intervention may affect outcomes of patients undergoing cardiac surgery, such as differences in postoperative morphine consumption, time to extubation, and length of hospital stay. Our results suggest that patients who receive preoperative intrathecal morphine have reduced postoperative systemic morphine consumption within 24 h. Length of hospital stay and time to extubation were not significantly different when compared to placebo. Although preoperative intrathecal morphine administration might be beneficial in this population, the quality of the data is low to make a recommendation. However, it may represent a potential add-on in the context of a multimodal pain management strategy for cardiac surgery.

CONCLUSION

Our study highlights the potential efficacy of preoperative intrathecal morphine administration in reducing postoperative morphine consumption 24 h after cardiac surgery. Although previous randomized controlled trials have already demonstrated the benefits of intrathecal morphine on postoperative opioid consumption, our meta-analysis gathered these studies to provide more definitive and conclusive evidence. Nevertheless, further studies are needed to investigate whether pre-emptive analgesia with intrathecal morphine can also result in lower pain scores and improved patient comfort during the perioperative period.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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