Systematic Review

Do Intrathecal Opioids Improve Surgical Outcomes After Coronary Artery Bypass Grafting? A Systematic Review and Analysis

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Background: Intrathecal opioids have long been used as analgesia for intractable cancer pain or as part of spinal anesthesia during obstetric operations. More recently, they have been used preoperatively as a pain management adjuvant for open cardiac and thoracic procedures.

Objective: This study aims to analyze the impact of administering intrathecal opioids before cardiac and thoracic surgeries on postoperative pain and mechanical ventilation.

Study design: Systematic review and meta-analysis.

Setting: University, School of Medicine, and several university-affiliated hospitals.

Methods: Five outcomes were studied, including the primary outcome of time to extubation, secondary outcomes of analgesia requirements at 24 and 48 hours, resting pain scores at 1 and 24 hours post-extubation, ICU length of stay in hours, and hospital length of stay in days. A search of multiple databases provided 28 studies reporting 4,000 total patients. Outcomes were measured using continuous mean difference with a 95% confidence interval, and the studies were examined for heterogeneity and sensitivity analysis.

Results: The primary outcome analysis suggested that time to extubation was 42 minutes shorter in the intrathecal opioid group (ranging from 82 to 1 minute, $P = 0.04$). There was also a decrease in postoperative analgesia requirements at both 24 hours (mean difference (MD) = -8.95 mg morphine equivalent doses (MED) [-9.4, -8.5], $P < 0.001$) and 48 hours (MD = -17.7 mg MED [-23.1, -12.4], $P < 0.001$) with I2 of 94% and 85% respectively, an improvement of pain scores at both 1 hour (MD = -2.24 [-3.16, -1.32], $P < 0.001$) and 24-hours (MD = -1.64 [-2.48, -0.80], $P =< 0.001$) I^2 of 94% and 85%, no change in both ICU length of stay (MD = -0.27 hours [-0.55, 0.01], $P = 0.06$) $I^2 = 77\%$ and hospital length of stay (MD = -0.30 days [-0.66, 0.06], $P = 0.11$) I2 = 32%.

Limitations: The major limitation of this meta-analysis was the inconsistent dosages of intrathecal opioids utilized. Some used the same dose for each patient, while other studies used weight-based doses. The differences in the outcomes observed may then be a result of the different amounts of opioids administered rather than the technique itself. Another limitation was the inconsistent timing of reports for pain scores and postoperative analgesic requirements. Further studies were analyzed at the 2 time periods for both secondary outcomes, making it difficult to attribute the 2 effects solely to the intervention.

Conclusions: We conclude that preoperative injection of intrathecal opioids is significantly associated with decreased time to extubation, decreased postoperative analgesia requirement, and improved pain scores. In controlled conditions with adequate staff education, this method of analgesia may make it possible to extubate the patients after the surgery in the operating room and fast-track their discharge from the hospital.

Key words: Analgesia, cardiac surgery, extubation, fast-tracking, hospital stay, spinal

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The neuraxial route of administering local anesthetic drugs was first described in the late 19th century by injecting cocaine into the epidural and subarachnoid spaces. Later, a Romanian surgeon, Nicolae Racoviceanu-Pitesti, was the first to use opioids intrathecally (1). This practice became more widespread in the 1940s. Still, it was not until opiate receptors were discovered in spinal tissue in 1973 that the proposed mechanism of action and scientific reasoning were found (2). To date, 5 types of opioid receptors are characterized: mu (MOR), kappa (KOR), delta (DOR), nociception (NOR), and zeta (ZOR). Besides ZOR, which serves its unique function in regulating tissue growth events, the other 4 receptors all play a crucial role in providing analgesia (3). Endogenous and exogenous opioid agonists bind to these G-protein coupled receptors to deactivate voltage-gated calcium channels and subsequently inhibit the presynaptic release of pain-associated excitatory neurotransmitters substance P and glutamate (4).

The intrathecal route of opioid administration has been well-established within the field of anesthesia and pain management, mainly owing to the ability to bypass the blood-brain barrier, requiring a lower dose to induce analgesic effects, thereby reducing the possibility of adverse effects associated with high systemic doses of analgesics (5). While intrathecal opioids have been around for decades and intensely studied, there has not been a clear, established role in other significant fields like cardiothoracic surgery. In recent decades, there has been considerable discord from other studies on whether using intrathecal opioids in patients undergoing cardiac surgery improves clinically relevant patient outcomes compared to systemic anesthesia. A 2004 meta-analysis by Liu et al concluded that when compared to general anesthesia, intrathecal analgesia "significantly hastens time until tracheal extubation when administered in small doses and reduces pain scores" following a coronary artery bypass graft (CABG) (6,7).

Conversely, a 2009 meta-analysis by Zangrillo et al concluded that spinal analgesia does not reduce perioperative morbidity and mortality after cardiac surgery (8). The results of this study strongly discourage the use of spinal analgesia to improve clinically relevant outcomes in patients undergoing cardiac surgery. However, these authors note that changes in techniques, devices, and drugs could modify the outlook of comparing spinal and standard anesthesia in this setting (8). Since this article's publication, significant developments have demanded changing landscape of analgesic techniques.

Administration of intrathecal opioids takes up OR time before surgery and would require additional hospital personnel and training. It also has side effects, such as headache, nausea, hypotension, and spinal hematoma (9). To determine if intrathecal opioid use should become an established part of the anesthetic plan before open cardiac surgeries, one must prove that there are multiple quantifiable clinical benefits for both the patient and the hospital. This study aims to analyze the effects of intrathecal anesthesia on clinical outcomes in patients undergoing cardiac surgery compared to general anesthesia. To address this question, the authors have independently conducted an updated systematic review and meta-analysis of pooled data from relevant studies. Studies were searched from PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and MEDLINE. The objectives are to address the impact of intrathecal opioids on the primary outcome variable of time to extubation and secondary outcomes such as postoperative pain scores, postoperative analgesia requirements, ICU length of stay, and the length of hospital stay.

Methods

Literature Retrieval/ Acquisition

This study follows the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA). We searched PubMed, Cochrane, MEDLINE, and Embase for published literature and excluded studies older than 25 years. No additional records were obtained manually. Keywords used in our search were "ICU Stay" OR "Hospital Stay" OR "Extubation time" OR "Pain Score" OR "Postoperative Analgesic Requirements" AND "Intrathecal Morphine" OR "Spinal Opioids" OR "Subarachnoid Anesthesia" AND "Coronary Artery Bypass Graft" OR "Cardiac Surgery" or "Thoracotomy." The study was exempted from further review by the local institutional review board, and no ethics committee approval was necessary since it uses only de-identified publicly available data (Suppl. Table 1).

Study Selection

We evaluated studies published as journal articles, randomized clinical trials, and retrospective cohort studies. Most "non-English" studies were excluded from the analysis due to the unavailability of a scientific interpreter that could reliably assess quantitative data. The primary outcome was time to extubation: secondary outcomes were pain scores, postoperative analgesic requirements expressed in morphine equivalent dose (MED) in milligrams, ICU length of stay, and hospital length of stay. Publications not including outcomes of interest were excluded. An initial screening by reviewers eliminated duplicates, studies with inconclusive data, and protocols that deviated from our defined parameters. The risk of bias for each study was assessed using the Cochrane Collaboration risk of bias tool.

Data Extraction

Data extracted for each study included the year of publication, the number of patients receiving intrathecal opioids and control group, intrathecal dosage, opioid type, and duration and outcomes of interest. A second reviewer evaluated all extracted data. Data were taken directly from the text of the study if available or derived from published graphs otherwise. Studies using non-morphine analgesia were converted into MEDs using Oregon Pain Guidance's Opioid Calculator.

Statistical Analysis

The data were analyzed and extracted using the RevMan 5.4.1 software (the Nordic Cochrane Centre, Copenhagen, Denmark). Our outcomes were continuous, evaluated using mean difference (MD) with a 95% confidence interval (CI), and an inverse variance statistical method was applied. Heterogeneity was assessed using the I^2 statistic, which describes the percentage of variation across studies due to heterogeneity rather than chance. A *P*-value of less than 0.05 provided evidence of a significant difference, and a *P*-value of less than 0.10 provided evidence for further assessment of heterogeneity. Forest plots were generated for data visualization by the same software. A random-effect analysis model was used for all variables with a heterogeneity ≥ 50%. The symmetry of the funnel plot analysis was used to evaluate a publication bias. In addition, we used the method described by Cochrane Handbook to convert the median and range into mean and standard deviations if raw data was unavailable in the reported study for calculations.

Results

Search Results

Four hundred ninety-one studies were discovered in the initial search. After removing duplicate publications, 175 studies were selected for abstract review. During the initial screening, we removed all case reports, review articles, most non-English studies, and studies with irretrievable full text. Forty-five studies qualified for full-text review. After the final screening, 28 studies reporting 4,000 patients met the inclusion criteria and were included in the meta-analysis. The PRISMA checklist was used to organize the review. The strategy for selecting eligible studies is provided (Suppl. Fig. 1).

The details for the included studies (i.e., publication date, study design, study region/country, number of patients in each group, age, gender, opioid type, dosage, and outcomes of interest) are summarized in Suppl. Table 2.

Time to Extubation

In 21 studies with 988 patients, the overall time to extubation was 4.15 hours (10-30). The time to extubation for patients that received intrathecal opioids before induction of anesthesia was 3.51 hours, while the time to extubation time was 4.76 hours for patients that did not. The mean difference between extubation times between the intrathecal groups and the control differed by -42 minutes, with a 95% CI ranging from -82 to -1 minute (*P* = 0.04) (Fig. 1).

The extubation times reported in these studies were considerably heterogeneous, with an I^2 of 92%. Six of these studies (4 RCTs and 2 observational studies) showed a clear benefit in using intrathecal opioids for fast-tracking patients that had undergone cardiac surgery, as shown by shorter times to extubation. In contrast, one study had shown that the use of intrathecal opioids was associated with a delay in extubation time. The remaining 11 studies show equivocal extubation times without a significant difference between the intrathecal opioid group and controls.

ICU Length of Stay

The length of stay (hours) was reported in 13 studies with 3,057 patients (10,12,14,15,17,21,23-25,31-33). No significant difference was found in ICU length of stay between patients receiving intrathecal opioids compared to control (MD = -6.5 hours [-13.2, 0.24 hours], *P* = 0.06). This data set was substantially heterogeneous, with I^2 = 77% (Fig. 2). Only 3 studies found significant decreases in ICU stay. The rest of the 10 studies reported no significant changes to the ICU length of stay with intrathecal opioid administration before induction of anesthesia.

Hospital Length of Stay

Hospital length of stay (days) was reported in 14 studies with 3,725 patients (12-17,21,23,24,31,32,34,35).

Study ID	E.S.	S.E.	P-Value	Lower	Upper
Alhashemi 2000	1.9	0.9	0.038	0.1	3.8
Alhashemi 2005	-1.2	1.1	0.276	-3.4	1.0
Bettex 2002	-1.8	0.6	0.001	-2.9	-0.7
Bhat 2021	-0.8	0.6	0.160	-1.9	0.3
Boulanger 2002	0.9	0.5	0.081	-0.1	1.9
Bowler 2002	-1.7	0.6	0.004	-2.9	-0.5
Chaney 1999	0.3	1.0	0.752	-1.6	2.2
Elgendy 2017	-0.8	1.6	0.620	-4.0	2.4
Elmiro 2021	-3.6	0.6	<.001	-4.8	-2.4
Jacobsohn 2005	0.0	0.2	0.823	-0.3	0.4
Latham 2000	-0.7	1.8	0.694	-4.2	2.8
Lena 2003	-1.8	0.5	<.001	-2.7	-0.8
Lena 2005	-1.9	0.5	<.001	-2.8	-1.0
Lena 2008	-1.9	0.4	<.001	-2.6	-1.2
Lenkutis 2002	1.3	0.2	<.001	0.9	1.6
Mehta 2004	-1.8	0.8	0.022	-3.3	-0.3
Mukherjee 2012	-0.1	0.4	0.836	-0.8	0.7
Parlow 2005	-1.5	0.1	<.001	-1.7	-1.2
Roediger 2006	0.0	0.6	0.988	-1.3	1.3
Turker 2005	0.4	0.4	0.328	-0.4	1.2
Yapici 2008	-1.3	0.6	0.037	-2.5	-0.1
Zarate 2000	-0.7	1.8	0.694	-4.2	2.8
Overall	**-0.8**	**0.3**	**0.012**	**-1.3**	**-0.2**

Model: Random-effects model
Heterogeneity: Tau-squared = 0.89, H-squared = 7.18, I-squared = 0.86
Homogeneity: Q = 262.33, df = 21, p-value < 0.001

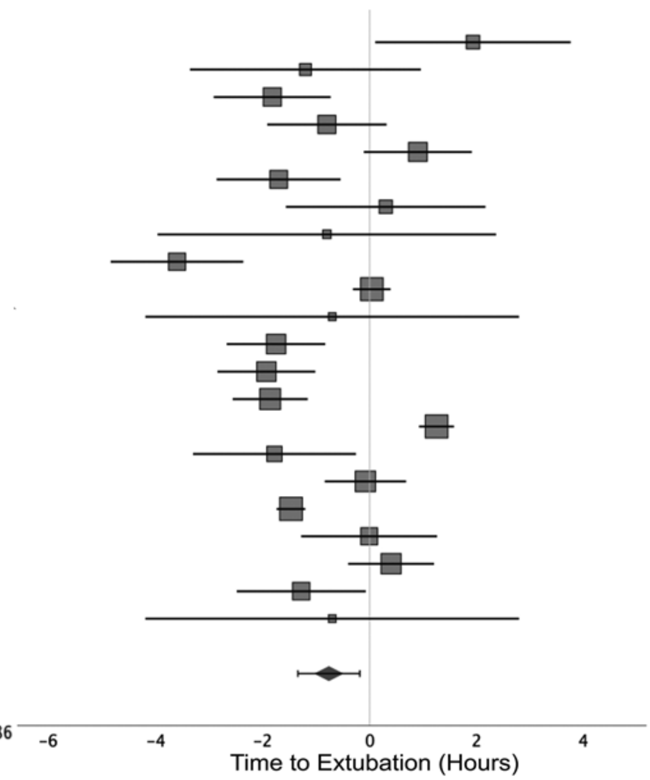


Fig. 1. *Forest plot examining the Time to Extubation of patients that received intrathecal opioids for their CABG compared to those that only received general anesthesia.*

Model: Random-effects model
Heterogeneity: Tau-squared = 240.87, H-squared = 40.37, I-squared = 0.98
Homogeneity: Q = 123.17, df = 11, p-value < 0.001

Study ID	E.S.	S.E.	P-Value	Lower	Upper	Wt (%)
Abidi 2013	-48.0	10.5	<.001	-68.6	-27.4	7.2
Alhashemi 2000	2.5	2.2	0.253	-1.8	6.8	10.3
Bowler 2002	15.0	13.2	0.256	-10.9	40.9	6.1
Elgendy 2017	-45.6	9.7	<.001	-64.5	-26.7	7.5
Ellenberger 2019	0.0	2.7	>.999	-5.3	5.3	10.2
Elmiro 2021	-12.0	9.4	0.200	-30.3	6.3	7.7
Hanada 2020	-12.5	0.8	0.000	-14.1	-10.9	10.4
Latham 2000	-4.8	4.8	0.317	-14.2	4.6	9.6
Mukherjee 2012	-4.0	28.7	0.889	-60.2	52.2	2.4
Roediger 2006	-3.0	6.9	0.663	-16.5	10.5	8.7
Türker 2004	3.0	4.7	0.523	-6.2	12.2	9.6
Yapici 2008	-3.1	1.1	0.005	-5.2	-0.9	10.4
Overall	**-8.8**	**5.2**	**0.116**	**-20.1**	**2.5**	

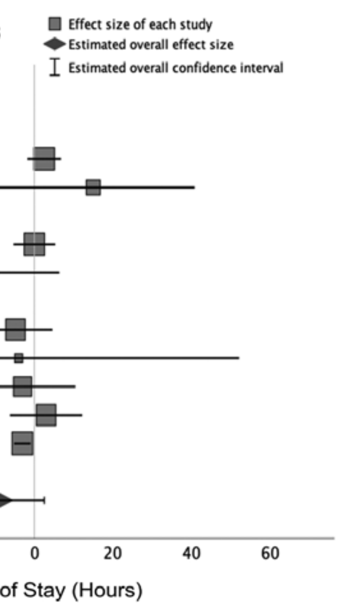


Fig. 2. *Forest plot examining the ICU Length of Stay of patients that received intrathecal opioids for their CABG compared to those that only received general anesthesia.*

No significant change was found in hospital length of stay in patients receiving intrathecal opioids compared to control (MD = -0.1 days [-0.6, 0.5]; $P = 0.110$; Fig. 3). The data set in this analysis was only modestly heterogenous with $I^2 = 32\%$. Only one observational study reported a reduction in the length of hospital stays with the administration of intrathecal opioids before induction of general anesthesia (31). The remaining 13 studies reported no significant benefits in the length of hospital stay.

Pain Scores at Rest

Using the 10 cm visual analog scale pain scores, pain control was recorded by 15 studies (11,12,14,18,23,24,26,32,36). For the same reason as post-op analgesic requirements, 9 studies with 1,000 patients were selected for pain score analysis at 1 hour post-extubation, and 10 studies with 471 patients were selected for pain score analysis at 24 hours post-extubation. Nine studies were included in both analyses. Pain scores were reported to be significantly lower in the intrathecal opioid group at both 1 hour (MD = -2.0 cm [-2.6, -1.3], $P < 0.001$) (Fig. 4A) and 24 hours (MD = -1.2 cm [-1.8, -0.50], $P = 0.001$) (Fig. 3B) post-extubation. Both sets of data were considerably heterogeneous, $I^2 = 94\%$ and $I^2 = 93\%$ at 1 and 24 hours, respectively. Five studies found that administration of intrathecal opioids before induction did not offer significant additional pain control one hour after extubation, and 7 studies did not find significant additional pain control 24 hours after extubation. The remaining 5 studies in both study groups reported significant pain control demonstrated as a reduction in pain scores.

Postoperative Analgesic Requirements

Of the eligible studies, 17 reported postoperative analgesic requirements for pain control as an outcome variable. Due to variations in timeframes of data collection, 13 studies with 2,845 patients were selected for a cumulative postoperative analgesic requirement analysis at 24 hours, and 7 studies with 1,259 patients were selected for a cumulative postoperative analgesic requirement analysis at 48 hours. Two studies were included in both analyses. Patients receiving intrathecal opioids were found to require significantly less MEDs of postoperative analgesia for pain control cumulatively at both 24 hours (MD = -14.0 mg-MED [-18.4, -9.6 mg-MED], $P < 0.001$) (Fig. 5A) and 48 hours (MD = -18.5 mg-MED [-26.5, -10.5 mg-MED], $P < 0.001$) (Fig. 5B). Both sets of data were considerably heterogeneous, $I^2 = 94\%$ and $I^2 = 85\%$ at 24 and 48 hours, respectively. Only one study found that intrathecal opioids before induction of anesthesia offered no clear benefit in terms of postoperative analgesic requirements. The remaining

Study ID	E.S.	S.E.	P-Value	Lower	Upper
Bowler 2002	6.0	3.5	0.088	-0.9	12.9
Chaney 2005	1.0	2.4	0.678	-3.7	5.7
Chaney 1999	0.1	0.9	0.909	-1.6	1.8
Dango	1.0	0.7	0.156	-0.4	2.4
Elgendy 2017	-2.0	3.2	0.532	-8.3	4.3
Ellenberger 2019	1.0	0.3	<.001	0.5	1.5
Elmiro 2021	-0.3	0.4	0.439	-1.1	0.5
Hanada 2020	-0.8	0.3	0.013	-1.4	-0.2
Jacobsohn 2005	-0.5	0.5	0.340	-1.5	0.5
Latham 2000	-0.4	0.6	0.502	-1.6	0.8
Mukherjee 2012	0.0	0.5	1.000	-0.9	0.9
Roediger 2006	-0.9	0.7	0.204	-2.3	0.5
Turker 2005	-0.6	0.7	0.396	-2.0	0.8
Vijitpavan 2002	0.0	0.2	1.000	-0.4	0.4
Overall	**-0.1**	**0.2**	**0.799**	**-0.6**	**0.5**

Model: Random-effects model
Heterogeneity: Tau-squared = 1.14, H-squared = 6.18, I-squared = 0.84
Homogeneity: Q = 29.78, df = 13, p-value = 0.01

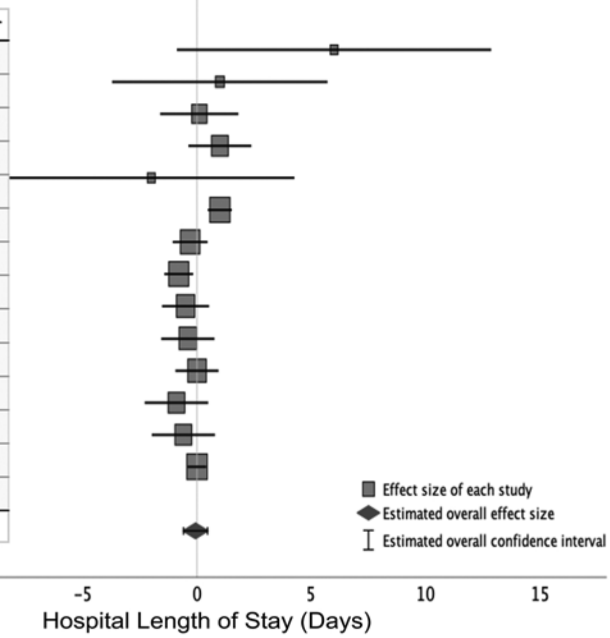


Fig. 3. *Forest plot examining the Hospital Length of Stay of patients that received intrathecal opioids for their CABG compared to those that only received general anesthesia.*

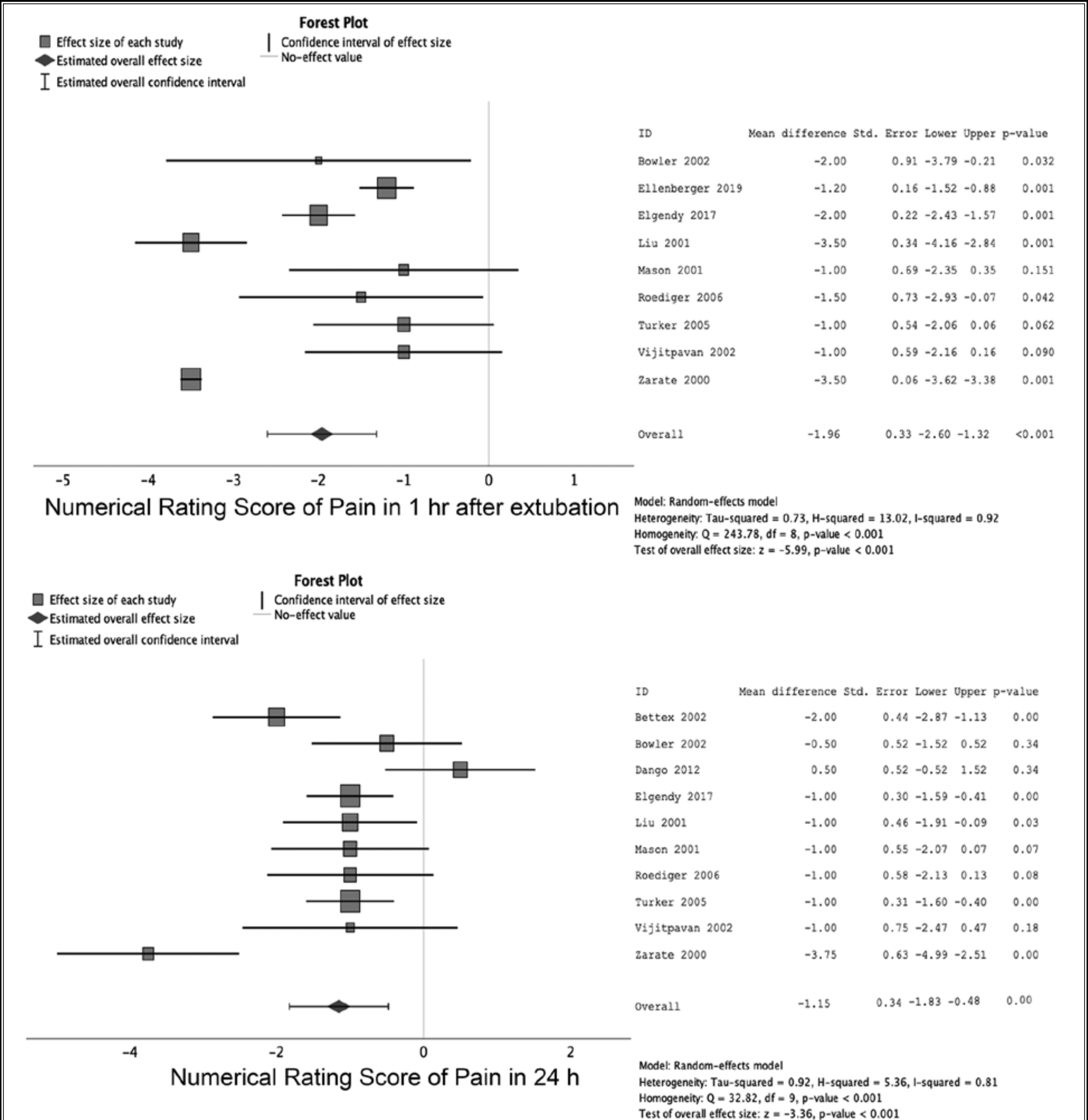


Fig. 4. *Forest plot examining the Pain Scores of patients that received intrathecal opioids for their CABG compared to those that only received general anesthesia one hour after extubation and twenty-four hours after extubation.*

15 papers all reported a significant reduction in the requirement for postoperative analgesia.

Discussion

Overall, the use of intrathecal opioids reduced extubation times in patients undergoing cardiac surgery. Moreover, it lowered pain scores and reduced the postoperative analgesia required for pain control. While this study did not find a significant reduction in ICU or hospital length of stay, previous studies have found that early extubation is associated with improved outcomes, including shorter ICU and hospital courses (37,38). In addition to increased patient satisfaction with pain control while using less analgesia, shorter extubation times offer benefits in lower risks for infections and complications related to mechanical ventilation. In this study, we find clear advantages to using intrathecal opioids before the induction of general anesthesia.

Fast-track care for cardiac surgical patients is a multidisciplinary approach aimed at improving the efficacy of care, of which early extubation is a major key (39). ICU or hospital length of stay is often used as an indirect cost measure, but complications contribute significantly. One study found that hospital costs were 119% higher on average for patients with complications than those without (40). Thus, reductions in time spent intubated directly affect the cost of healthcare. We find the injection of intrathecal opioids, having reduced the time to extubation by 42 minutes, demonstrating value in patient outcomes and hospital savings.

Pain score reduction slightly lessened from 1 to 24 hours post-extubation (-2.0 cm vs. -1.2 cm). This was anticipated as the effects of the intrathecal injections wean over time, tolerance builds, and perception of pain is altered. However, reductions in postoperative analgesic requirements approximately doubled from 24 to 48 hours post-extubation (-14 mg-MED vs. -18.5 mg-MED), maintaining a relatively constant decrease in analgesia consumption per day, suggestive of an enduring pain control effect. It is worth noting that different studies were utilized to analyze pain scores and postoperative analgesic requirements at each time period recorded due to inconsistent reporting. Thus, it is difficult to completely attribute either observation to the administration of intrathecal opioids (41). Further research areas might look into the evolution of pain scores over time rather than 2 points in time.

Conclusion

In conclusion, intrathecal opioids remain an attractive option for analgesia following cardiac surgery due to their utility in fast-track cardiac care. Extubation times were reduced by 42 minutes, mitigating mechanical ventilator-associated infections and complications. Patients experienced lower pain scores despite requiring less analgesia. We suspect that intrathecal opioid administration will benefit patient experience and hospital cost savings associated with shorter intubation time.

Supplemental material available at www.painphysicianjournal.com

References

1. Brill S, Gurman GM, Fisher A. A history of neuraxial administration of local analgesics and opioids. *Eur J Anaesthesiol* 2003; 20:682-689.
2. Pert CB, Snyder SH. Opiate receptor: Demonstration in nervous tissue. *Science* 1973; 179:1011-1014.
3. Dhaliwal A, Gupta M. Physiology, opioid receptor. In: *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing; 2021. www.ncbi.nlm.nih.gov/books/NBK546642/
4. Rawal N, Allvin R. Epidural and intrathecal opioids for postoperative pain management in Europe--a 17-nation questionnaire study of selected hospitals. Euro Pain Study Group on Acute Pain. *Acta Anaesthesiol Scand*. 1996; 40:1119-1126.
5. Nader ND, Li CM, Dosluoglu HH, Ignatowski TA, Spengler RN. Adjuvant therapy with intrathecal clonidine improves postoperative pain in patients undergoing coronary artery bypass graft. *Clin J Pain* 2009; 25:101-106.
6. Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: A meta-analysis. *Anesthesiology* 2004; 101:153-161.
7. Bignami E, Landoni G, Biondi-Zoccai GG, al. Epidural analgesia improves outcome in cardiac surgery: A meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2010; 24:586-597.
8. Zangrillo A, Bignami E, Biondi-Zoccai GG, et al. Spinal analgesia in cardiac surgery: A meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2009; 23:813-821.
9. Hyderally H. Complications of spinal anesthesia. *Mt Sinai J Med* 2002; 69:55-56.
10. Alhashemi JA, Sharpe MD, Harris CL, Sherman V, Boyd D. Effect of subarachnoid morphine administration on extubation time after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2000; 14:639-644.
11. Bettex DA, Schmidlin D, Chassot PG, Schmid ER. Intrathecal sufentanil-morphine shortens the duration of intubation and improves analgesia in fast-track cardiac surgery. *Can J Anaesth*. 2002; 49:711-717.
12. Bowler I, Djaiani G, Abel R, Pugh S, Dunne J, Hall J. A combination of intrathecal morphine and remifentanil anesthesia for fast-track cardiac anesthesia and surgery. *J Cardiothorac Vasc Anesth* 2002; 16: 709-714.
13. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Intrathecal morphine for coronary artery bypass graft procedure and early extubation revisited. *J Cardiothorac Vasc Anesth* 1999; 13:574-578.
14. Elgendy H, Helmy HAR. Intrathecal morphine improves hemodynamic parameters and analgesia in patients undergoing aortic valve replacement surgery: A prospective, double-blind, randomized trial. *Pain Physician* 2017; 20:405-412.
15. Elmiro GS, Souza AH, Loyola SO, et al. Spinal anesthesia increases the frequency of extubation in the

operating room and decreases the time of mechanical ventilation after cardiac surgery. *Braz J Cardiovasc Surg* 2021; 36:32-38.

16. Jacobsohn E, Lee TW, Amadeo RJ, et al. Low-dose intrathecal morphine does not delay early extubation after cardiac surgery. *Can J Anaesth* 2005; 52:848-857.
17. Latham P, Zarate E, White PF, et al. Fast-track cardiac anesthesia: A comparison of remifentanil plus intrathecal morphine with sufentanil in a desflurane-based anesthetic. *J Cardiothorac Vasc Anesth* 2000; 14:645-651.
18. Lena P, Balarac N, Arnulf JJ, Teboul J, Bonnet F. Intrathecal morphine and clonidine for coronary artery bypass grafting. *Br J Anaesth* 2003; 90:300-303.
19. Lenkutis T, Bieliūnas A, Gedminaite I. [Intrathecal morphine for postoperative analgesia in cardiac surgery]. *Medicina (Kaunas)* 2002; 38 Suppl 2:221-223.
20. Mehta Y, Kulkarni V, Juneja R, et al. Spinal (subarachnoid) morphine for off-pump coronary artery bypass surgery. *Heart Surg Forum* 2004; 7:E205-E210.
21. Mukherjee C, Koch E, Banusch J, Scholz M, Kaisers UX, Ender J. Intrathecal morphine is superior to intravenous PCA in patients undergoing minimally invasive cardiac surgery. *Ann Card Anaesth* 2012; 15:122-127.
22. Parlow JL, Steele RG, O'Reilly D. Low dose intrathecal morphine facilitates early extubation after cardiac surgery: Results of a retrospective continuous quality improvement audit. *Can J Anaesth* 2005; 52:94-99.
23. Roediger L, Joris J, Senard M, Larbuisson R, Canivet JL, Lamy M. The use of pre-operative intrathecal morphine for analgesia following coronary artery bypass surgery. *Anaesthesia* 2006; 61:838-844.
24. Turker G, Goren S, Sahin S, Korfali G, Sayan E. Combination of intrathecal morphine and remifentanil infusion for fast-track anesthesia in off-pump coronary artery bypass surgery. *J Cardiothorac Vasc Anesth*. 2005; 19:708-713.
25. Yapici D, Altunkan ZO, Atici S, et al. Postoperative effects of low-dose intrathecal morphine in coronary artery bypass surgery. *J Card Surg* 2008; 23:140-145.
26. Zarate E, Latham P, White PF, et al. Fast-track cardiac anesthesia: Use of remifentanil combined with intrathecal morphine as an alternative to sufentanil during desflurane anesthesia. *Anesth Analg*. 2000; 91:283-287.
27. Bhat I, Arya VK, Mandal B, Jayant A, Dutta V, Rana SS. Postoperative hemodynamics after high spinal block with or without intrathecal morphine in cardiac surgical patients: A randomized-controlled trial. *Can J Anaesth* 2021; 68:825-834.
28. Boulanger A, Perreault S, Choiniere M, Prieto I, Lavoie C, Laflamme C. Intrathecal morphine after cardiac surgery. *Ann Pharmacother* 2002; 36:1337-1343.
29. Lena P, Balarac N, Arnulf JJ, Bigeon JY, Tapia M, Bonnet F. Fast-track coronary artery bypass grafting surgery under general anesthesia with remifentanil and spinal analgesia with morphine and clonidine. *J Cardiothorac Vasc Anesth* 2005; 19:49-53.
30. Lena P, Balarac N, Lena D, et al. Fast-track anesthesia with remifentanil and spinal analgesia for cardiac surgery: The effect on pain control and quality of recovery. *J Cardiothorac Vasc Anesth* 2008; 22:536-542.
31. Hanada S, Kurosawa A, Randall B, Van Der Horst T, Ueda K. Impact of high spinal anesthesia technique on fast-track strategy in cardiac surgery: Retrospective study. *Reg Anesth Pain Med* 2020; 45:22-26.
32. Ellenberger C, Sologashvili T, Bhaskaran K, Licker M. Impact of intrathecal morphine analgesia on the incidence of pulmonary complications after cardiac surgery: A single center propensity-matched cohort study. *BMC Anesthesiology* 2017; 17:109-115.
33. Abidi S, Frigui W, Bouzouita W, Chemchikh H, Marzouk M, Kortas C. Ultra-fast-track cardiac anesthesia: 4AP2-6. *Eur J Anaesthesiol* 2013; 30:59-60.
34. Chaney MA. Cardiac surgery and intrathecal/epidural techniques: At the crossroads? *Can J Anaesth* 2005; 52:783-788.
35. Vijitpavan A, Kittikunakorn N, Komonhirun R. Comparison between intrathecal morphine and intravenous patient control analgesia for pain control after video-assisted thoracoscopic surgery: A pilot randomized controlled study. *PLoS One* 2022; 17:e0266324.
36. Mason N, Gondret R, Junca A, Bonnet F. Intrathecal sufentanil and morphine for post-thoracotomy pain relief. *Br J Anaesth* 2001; 86:236-240.
37. Li Y, Jia Y, Wang H, et al. Early extubation is associated with improved outcomes after complete surgical repair of pulmonary atresia with ventricular septal defect and hypoplastic pulmonary arteries in pediatric patients. *J Cardiothorac Surg* 2021; 16:31-36.
38. Badhwar V, Esper S, Brooks M, et al. Extubating in the operating room after adult cardiac surgery safely improves outcomes and lowers costs. *J Thorac Cardiovasc Surg* 2014; 148:3101-3109.e1.
39. Cheng DC. Fast track cardiac surgery pathways: Early extubation, process of care, and cost containment. *Anesthesiology* 1998; 88:1429-1433.
40. Healy MA, Mullard AJ, Campbell DA Jr, Dimick JB. Hospital and payer costs associated with surgical complications. *JAMA Surg* 2016; 151:823-830.
41. Wong WT, Lai VK, Chee YE, Lee A. Fast-track cardiac care for adult cardiac surgical patients. *Cochrane Database Syst Rev* 2016; 9:CD003587.

Supplemental Table 1: ***PubMed, Cochrane, Embase, and Medline. 1997-2022***

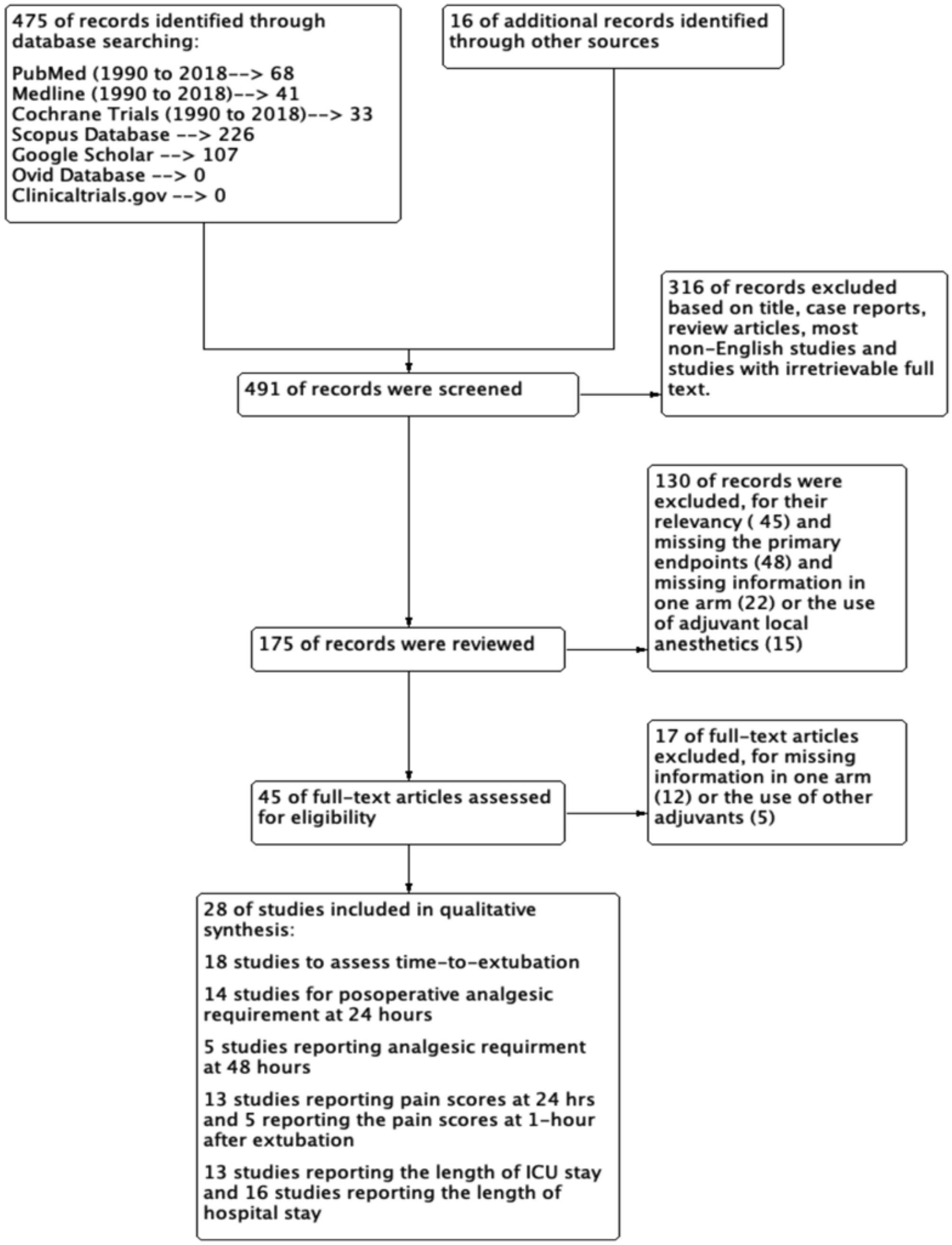
	Exposure	**Modifier**	**Outcome**
OR	Cardiothoracic Surgery Thoracic Surgery Cardiac Surgery Vascular Surgery Open Heart Surgery Aneurysm Repair Heart Transplant Thoracotomy CABG Coronary Artery Bypass Grafting Coronary Artery Bypass Coronary revascularization Myocardial Revascularization Valve Replacement Surgery Mitral Valve Replacement/ Repair Aortic Valve Replacement/ Repair Tricuspid Valve Replacement/ Repair Pulmonary Valve Replacement/ Repair Valve Repair Surgery	Spinal Opioid Intrathecal Opioid Intrathecal Morphine Intrathecal Fentanyl Intrathecal Diamorphine Intrathecal Hydromorphone Intrathecal Sufentanil Intrathecal Methadone Spinal Anesthesia Intrathecal Anesthesia Intrathecal Lidocaine Intrathecal Bupivacaine Intrathecal Levobupivacaine Intrathecal Ropivacaine Intrathecal Chloroprocaine Neuraxial Anesthesia Intrathecal Injection Spinal Injection Intraspinal Injection Subarachnoid Anesthesia	Fast Track Hospital Length (of Stay) Intensive Care (unit) Length (of Stay) Pain Score (NRS, VAS) Raw (PSEQ) score Postoperative analgesia Rescue Analgesia Sedation Score Intubation Time Extubation Time Time to Extubation Pulmonary Function Pulmonary Ventilation Minute Ventilation Respiratory Airflow Rapid Shallow Breathing Index Tidal Volume Oxygenation Hospital readmission

Supplemental Table 2. *Details of the studies included in this analysis.*

Author	Year	Title	Study Size	Study Design	ITM Dosage	Co-Administered #1	Surgery Type
Vijitpavan	2022	Comparison between intrathecal morphine and intravenous patient control analgesia for pain control after video-assisted thoracoscopic surgery: A pilot randomized controlled study	28	RCT	200 µg		Video-assisted Thoracoscopic Surgery (VATS)
Elmiro	2021	Spinal Anesthesia Increases the Frequency of Extubation in the Operating Room and Decreases the Time of Mechanical Ventilation after Cardiac Surgery	217	Observational	3 µg/kg	20-25 µg Sufentanil; 6-8 mL Bupivacaine	Cardiac Surgery
Hanada	2020	Impact of high spinal anesthesia technique on fast-track strategy in cardiac surgery: retrospective study	1025	Observational			Elective Cardiac Surgery
Ellenberger	2017	Impact of intrathecal morphine analgesia on the incidence of pulmonary complications after cardiac surgery: a single center propensity-matched cohort study	1003	Observational	10 µg/kg		Elective Cardiac Surgery
Elgendy	2017	Intrathecal Morphine Improves Hemodynamic Parameters and Analgesia in Patients Undergoing Aortic Valve Replacement Surgery: A Prospective, Double-Blind, Randomized Trial	44	RCT	7 µg/kg		Aortic Valve Replacement
Goldie	2014	Perioperative outcomes of high spinal anesthesia for cardiac surgery	306	Observational			
Abidi	2013	Ultra-fast-track cardiac anesthesia	80	Observational			
Dango	2012	Combined paravertebral and intrathecal vs thoracic epidural analgesia for post-thoracotomy pain relief	80	RCT	4-5 µg/kg	0.2-0.3 µg/kg Sufentanil	
Mukherjee	2012	Intrathecal morphine is superior to intravenous PCA in patients undergoing minimally invasive cardiac surgery	61	RCT	1.5 µg/kg		
Zeid	2012	Comparison between intrathecal morphine with paravertebral patient controlled analgesia using bupivacaine for intraoperative and post-thoracotomy pain relief	40	RCT	300 µg		
McAnulty	2010	Does intrathecal diamorphine improve pain relief after thoracic surgery?	334	Observational	300 µg **morphine**		
Mertin	2009	Total spinal anesthesia for cardiac surgery: does it make a difference in patient outcomes?	120	Observational			
dos Santos	2009	Intrathecal morphine plus general anesthesia in cardiac surgery: effects on pulmonary function, postoperative analgesia, and plasma morphine concentration	42	RCT	400 µg		Cardiac Surgery
Yapici	2008	Postoperative effects of low-dose intrathecal morphine in coronary artery bypass surgery	23	RCT	7 µg/kg		
Askar	2007	The efficacy of intrathecal morphine in post-thoracotomy pain management	33	RCT	10 µg/kg		Thoracotomy
Roediger	2006	The use of pre-operative intrathecal morphine for analgesia following coronary artery bypass surgery	30	RCT	500 µg		Coronary Artery Bypass Graft
Parlow	2005	Low dose intrathecal morphine facilitates early extubation after cardiac surgery: results of a retrospective continuous quality improvement audit	131	Observational	<5 µg/kg		Cardiac Surgery
Turker	2005	Combination of intrathecal morphine and remifentanil infusion for fast-track anesthesia in off-pump coronary artery bypass surgery	43	RCT	10 µg/kg	Remifentanil	
Jacobsohn	2005	Low-dose intrathecal morphine does not delay early extubation after cardiac surgery	43	RCT	6 µg/kg		Coronary Artery Bypass Graft

Supplemental Table 2 cont. *Details of the studies included in this analysis*.

Author	Year	Title	Study Size	Study Design	ITM Dosage	Co-Administered #1	Surgery Type
Boulanger	2002	Intrathecal morphine after cardiac surgery	42	RCT	20μg/kg - 1000μg		
Lenkutis	2002	[Intrathecal morphine for postoperative analgesia in cardiac surgery]	37	RCT			
Bowler	2002	A combination of intrathecal morphine and remifentanil anesthesia for fast-track cardiac anesthesia and surgery	24	RCT	2000μg	1μg Remifentanil bolus and 0.25-1 μg/kg/min	
Bettex	2002	Intrathecal Sufentanil-morphine shortens the duration of intubation and improves analgesia in fast-track cardiac surgery	24	RCT	500 μg	50 μg Sufentanil	
Mason	2001	Intrathecal Sufentanil and morphine for post-thoracotomy pain relief	30	RCT	200 μg	20 μg Sufentanil	Thoracotomy
Liu	2001	A randomized, double-blinded comparison of intrathecal morphine, Sufentanil and their combination versus IV morphine patient-controlled analgesia for post thoracotomy pain	30	RCT	500 μg		
Alhashemi	2000	Effect of subarachnoid morphine administration on extubation time after coronary artery bypass graft surgery	50	RCT			
Latham	2000	Fast-track cardiac anesthesia: a comparison of remifentanil plus intrathecal morphine with sufentanil in a desflurane-based anesthetic	40	RCT	8 μg/kg		Coronary Artery Bypass Graft
Chaney	1996	Large-dose intrathecal morphine for coronary artery bypass grafting	40	RCT	4 mg		



Supplemental Fig. 1. *PRISMA flow diagram for the study selection*.