ANESTHESIOLOGY

Intrathecal Morphine for Analgesia in Minimally Invasive Cardiac Surgery: A Randomized, Placebo-controlled, Double-blinded Clinical Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The optimal strategy for acute pain management after minimally invasive cardiac surgery has not been defined
- Intrathecal opioids provide effective postoperative analgesia in many settings

What This Article Tells Us That Is New

- Used at a dose of 5 mcg/kg, intrathecal morphine reduced opioid consumption approximately 50% during the first 24 postoperative hours
- Additionally, intrathecal morphine reduced pain at rest and with cough for 48 h, although mild nausea was more common among those receiving morphine than those receiving sham saline injections

ABSTRACT

Background: Intrathecal morphine decreases postoperative pain in standard cardiac surgery. Its safety and effectiveness have not been adequately evaluated in minimally invasive cardiac surgery. The authors hypothesized that intrathecal morphine would decrease postoperative morphine consumption after minimally invasive cardiac surgery.

Methods: In this randomized, placebo-controlled, double-blinded clinical trial, patients undergoing robotic totally endoscopic coronary artery bypass received either intrathecal morphine (5 mcg/kg) or intrathecal saline before surgery. The primary outcome was postoperative morphine equivalent consumption in the first 24 h after surgery; secondary outcomes included pain scores, side effects, and patient satisfaction. Pain was assessed *via* visual analog scale at 1, 2, 6, 12, 24, and 48 h after intensive care unit arrival. Opioid-related side effects (nausea/vomiting, pruritus, urinary retention, respiratory depression) were assessed daily. Patient satisfaction was evaluated with the Revised American Pain Society Outcome Questionnaire.

Results: Seventy-nine patients were randomized to receive intrathecal morphine (n = 37) or intrathecal placebo (n = 42), with 70 analyzed (morphine 33, placebo 37). Intrathecal morphine patients required significantly less median (25th to 75th percentile) morphine equivalents compared to placebo during first postoperative 24 h (28 [16 to 46] mg *vs.* 59 [41 to 79] mg; difference, –28 [95% CI, –40 to –18]; $P < 0.001$) and second postoperative 24 h (0 [0 to 2] mg *vs.* 5 [0 to 6] mg; difference, –3.3 [95% CI, –5 to 0]; $P < 0.001$), exhibited significantly lower visual analog scale pain scores at rest and cough at all postoperative timepoints (overall treatment effect, –4.1 [95% CI, –4.9 to –3.3] and –4.7 [95% CI, –5.5 to –3.9], respectively; $P < 0.001$), and percent time in severe pain (10 [0 to 40] *vs.* 40 [20 to 70]; $P = 0.003$) during the postoperative period. Mild nausea was more common in the intrathecal morphine group (36% *vs.* 8%; $P = 0.004$).

Conclusions: When given before induction of anesthesia for totally endoscopic coronary artery bypass, intrathecal morphine decreases use of postoperative opioids and produces significant postoperative analgesia for 48 h.

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Coronary artery bypass grafting (CABG) is traditionally performed *via* median sternotomy. In an attempt to avoid sternotomy, minimally invasive cardiac surgery was popularized in the 1990s (anterior minithoracotomy). Rapid clinical development of robotic telemanipulation in the late 1990s led to the creation of robotic cardiac surgery, a subset of which is totally endoscopic CABG, performed robotically *via* multiple thoracic ports.[1]

Inadequate postoperative analgesia has the potential to initiate pathophysiologic changes in all major organ systems, which may lead to substantial morbidity, including chronic pain syndromes.[2–4] While median sternotomy pain may be severe, pain after minimally invasive cardiac surgery (anterior minithoracotomy and/or robotic thoracic ports) seems consistently more intense and challenging to control.[5,6] In the current era of enhanced recovery

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after surgery, adequate postoperative analgesia allowing immediate tracheal extubation is oftentimes difficult to achieve in patients undergoing minimally invasive cardiac surgery.[7,8]

As minimally invasive cardiac surgery has become increasingly utilized, numerous regional analgesic techniques have been applied without reliable success.[5,6,9,10] Reasons for inconsistency include the wide variety of thoracic incisions used and technical difficulty/unreliability of the regional techniques. Intrathecal morphine has numerous potential advantages during minimally invasive cardiac surgery, yet has not been adequately evaluated in the current enhanced recovery after surgery era. In this randomized, placebo-controlled, double-blinded clinical investigation, we hypothesize that 5 mcg/kg intrathecal morphine in patients undergoing robotic totally endoscopic CABG with immediate tracheal extubation (operating room/immediate postoperative period) will decrease postoperative morphine consumption.

Materials and Methods

This clinical trial was approved by the University of Chicago (Chicago, Illinois) Institutional Review Board (IRB) and was registered at Clinicaltrials.gov (NCT03241485) on August 7, 2017, before patient enrollment (principal investigator: Richa Dhawan, M.D., M.P.H.). This article conforms to the Consolidated Standards of Reporting Trials guidelines. The trial was conducted in adherence to the original protocol, which is available upon request. This randomized, placebo-controlled, double-blinded clinical trial was conducted at the University of Chicago Medical Center. Patients were screened for eligibility, and informed consent was obtained on day of surgery in the preoperative area by a member of the study team. Inclusion criteria were patients undergoing elective totally endoscopic CABG without anticipated cardiopulmonary bypass (CPB) support and with anticipated intraoperative extubation. Exclusion criteria included emergency surgery, anticipated CPB support, anticipated postoperative extubation, previous cardiothoracic surgery, left ventricular ejection fraction less than 40%, preoperative cardiac support (IV inotropes and/or vasoconstrictors/intra-aortic balloon pump), severe pulmonary disease (home oxygen requirement and/or recent steroid use), renal dysfunction (serum creatinine greater than 1.5 mg/dl), hepatic impairment, preoperative opioid use and/or history of opioid abuse, morbid obesity (body mass index greater than 35 kg/m^2), and any contraindication to intrathecal injection (morphine allergy, coagulopathy, patient refusal). Selected exclusion criteria reflect patient characteristics that would not likely allow for immediate tracheal extubation and assessment of pain scores. The primary outcome is postoperative morphine equivalent consumption in the first 24 h after surgery. Secondary outcomes include postoperative pain scores, opioid-related side effects, and self-reported patient satisfaction.

After written informed consent, patients were randomized to receive either intrathecal morphine (5 mcg/kg, morphine group) or intrathecal placebo (sterile saline, placebo group). Based on previous clinical trials, the dose of intrathecal morphine was selected to potentially facilitate postoperative analgesia without hindering immediate extubation.[11,12]

Before study commencement, a study statistician created a computer-generated randomization list (using simple randomization) to allocate study arm assignments in a 1:1 ratio, which was provided to an operating room pharmacist who prepared the appropriate intrathecal solution. On the day of surgery, the principal investigator (R.D.) assessed the patient for eligibility, obtained informed consent, and enrolled the participant in the trial. After informed consent, the pharmacist, based on the sequentially numbered randomization list, prepared either a placebo or a morphine syringe. Ultimately, a 3-ml syringe (total volume, 1 ml clear solution) was delivered to the anesthesia caregiver. All syringes, regardless of saline or morphine solution, appeared identical. All caregivers were blinded to group assignment throughout hospital stay.

Both groups were treated identically during the preoperative/intraoperative period. Following application of standard American Society of Anesthesiologists (Schaumburg, Illinois) monitors and achieving IV access, 1 mg IV midazolam was given, and the patient assumed the sitting position. After normal prepping/draping and local infiltration with lidocaine, a 24-gauge Sprotte (Germany) needle was inserted *via* the L3–L4 or L4–L5 interspace (introducer-assisted) under sterile conditions. Upon free return of clear cerebrospinal fluid, the 1-ml study solution was injected and the Sprotte needle removed. The patient then assumed the supine position, a radial arterial line was inserted, and general anesthesia was induced.

The intraoperative anesthetic technique was standardized in all patients. Induction consisted of IV midazolam (2 to 4 mg), sufentanil (0.5 mcg/kg), propofol (1 mg/kg), and rocuronium (0.6 mg/kg). After intubation, inhaled desflurane was adjusted to maintain a Bispectral Index (BIS system; USA) value of 40 to 60 and a mean arterial blood pressure within 20% baseline value. Supplemental propofol and rocuronium were allowed throughout, consistent with the goal of intraoperative extubation. A single-lumen endotracheal tube (8.0) was used, through which either an Arndt Blocker (Cook Critical Care; USA) or EZ-Blocker (Teleflex Life Sciences Ltd.; Ireland) was inserted and positioned *via* fiberoptic guidance to facilitate one-lung ventilation when required. While on two-lung ventilation, mechanical ventilation parameters were standardized (tidal volume, 5 ml/kg ideal body weight; respiratory rate appropriate for normocarbia, fractional inspired oxygen tension 100%; and positive end-expiratory pressure, 5 cm H_2O). Postinduction, a 9 French double-lumen introducer was inserted *via* the right internal jugular vein, and

intraoperative transesophageal echocardiography was used throughout.

All patients underwent totally endoscopic CABG without CPB support *via* standard robotic thoracic ports (fig. 1) and the DaVinci surgical system (DaVinci, Intuitive Surgical; USA). The left and/or right internal thoracic arteries served as conduits. Typically, IV heparin was administered (100 to 150 U/kg; activated clotting time goal, 250 s) before distal anastomoses, which was ultimately reversed with IV protamine (1 mg/100 U heparin). All patients had thoracic port incisions injected with 0.25% bupivacaine (30 ml total divided volume) at the conclusion of surgery. Once surgery was finished, consultation between the attending surgeon and anesthesiologist determined timing of attempted extubation (intraoperative or immediately postoperative). If intraoperative extubation was attempted, IV sugammadex (2 mg/kg) and ondansetron (4 mg) were administered. IV ketorolac (15 mg) was allowed if emergence tachycardia/hypertension occurred. Extubation was accomplished once specific criteria were met (appendix 1). IV fentanyl was allowed if clinically indicated (pain) before transport to the intensive care unit (ICU).

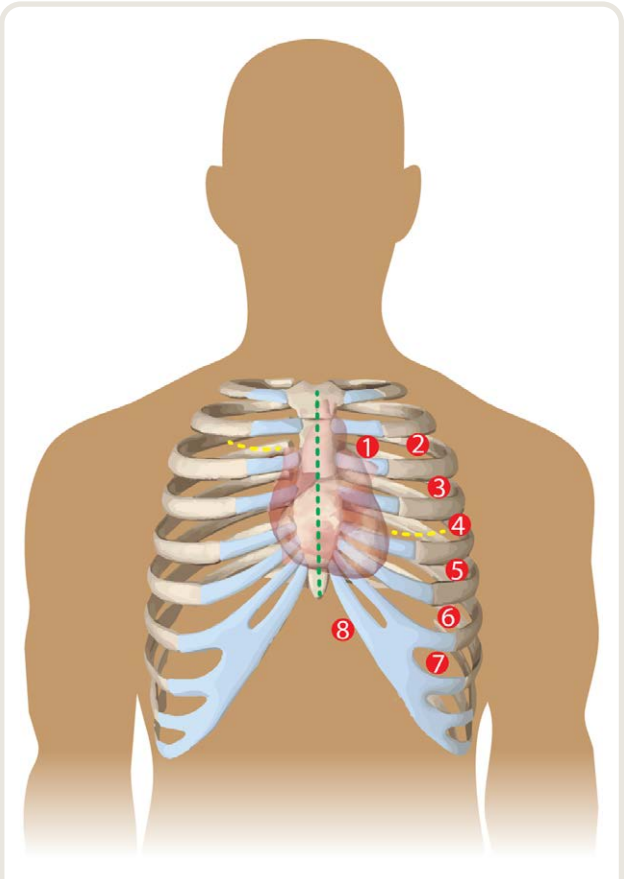

Fig. 1. Incisions used during minimally invasive cardiac surgery. Robotic port sites (*red circles*) in the majority of patients; second anterior intercostal space (*1*) is the accessory site with a 12-mm port, second (*2*) interspace is a 8-mm right arm port, fourth (*4*) interspace is a 12-mm camera port, the sixth (*6*) interspace is a 8-mm left arm port, and a subcostal (*8*) site is a 12-mm port for the stabilizer. Another variation is the use of interspaces *3*, *5*, and *7* instead of *2*, *4*, and *6*. *Green line*, median sternotomy; *yellow line*, anterior minithoracotomy (mitral/aortic valve).

Postoperative care was standardized in all patients. Patients not undergoing intraoperative extubation were extubated at the earliest clinically appropriate time in the ICU once the same specific intraoperative extubation criteria were met (appendix 1). The dates of patient enrollment in the clinical trial were June 19, 2018, to August 31, 2020. Postoperative analgesic technique in the ICU consisted of IV fentanyl (25 mcg as needed) initially (June 19, 2018, to February 8, 2019), then transitioned to IV morphine (patient-controlled analgesia [PCA] pump: 2 mg dose, lockout interval 8 min) later (February 19, 2019, to August 31, 2020). The reason for this transition was that the University of Chicago experienced an IV morphine drug shortage/unavailability during the initial period of the study. During the entire study period, IV fentanyl (25 mcg), IV ketorolac (15 mg every 6 h, maximum four doses), and/or IV hydromorphone was administered in the ICU, if needed. Once discharged to the surgical ward, all patients received oral hydrocodone-acetaminophen (5 to 325 mg), oxycodone (5 mg), and/or tramadol (50 mg), if needed. Morphine equivalents were then calculated as previously described.[13] Equivalent doses to 1.0 mg IV morphine and conversion factors used for specific drugs were IV fentanyl (0.01 mg/0.10), IV hydromorphone (0.15 mg/6.70), oral hydrocodone (3.0 mg/0.30), oral oxycodone (2.0 mg/0.50), and oral tramadol (15 mg/0.06).

Data Collection

Data were collected by research team members and nurses who were blinded to group assignment. Preoperative data were collected from electronic medical records. Postoperatively, a data collection sheet was given to ICU/surgical ward nurses to capture secondary outcomes. In addition, patient electronic medical records were accessed for verification. Pain was evaluated in the ICU and surgical ward per nurse at 1, 2, 6, 12, 24, and 48 h after ICU admission *via* a visual analog scoring system (0 to 10 scale, 0 = no pain, 10 = worst pain imaginable) at rest and with cough.

Opioid-related side effects (nausea/vomiting, pruritus, urinary retention, and respiratory depression) were evaluated in all patients daily by nurses until hospital discharge. Patients were questioned regarding occurrence of nausea/vomiting and pruritus. Urinary retention was defined as need for reinsertion of a urinary catheter or straight catherization after Foley catheter removal. Opioid-specific respiratory depression was defined as prolonged tracheal reintubation secondary to hypercarbia (arterial blood gas analysis) and/or escalation of respiratory support after extubation thought to be secondary to hypercarbia.

Before hospital discharge, patients completed the Revised American Pain Society Outcome Questionnaire, which evaluates subjective experiences of pain after surgery.[14]

Power Analysis/IRB Termination

Recent clinical research indicates that when comparing two different intraoperative anesthetic techniques in patients undergoing cardiac surgery, a reduction in postoperative morphine requirements during the initial 24 h from a median of 10 mg to 6 mg was observed.[15] With a one-sided significance level of 0.05 and anticipated 5 mg mean difference (SD of 8 mg), calculated power was 96% for 120 patients total (60 per group). Initial IRB approval was for study inclusion of 120 patients (60 per group).

Interim analysis of data for presentation in abstract form yielded statistically significant differences between the two groups regarding primary and secondary outcomes. Thus, on September 21, 2020, the IRB chose to permanently close the study for enrollment because "the primary endpoint of this study had been met with statistical significance with fewer number of subjects than what was originally planned."

Statistical Analysis

Variables were summarized as mean ± SD for normally distributed continuous variables, median (25th to 75th percentile) for continuous variables with evidence of nonnormality or for ordinal variables, and frequency counts and percentages for categorical variables. For the primary outcome (amount of postoperative morphine use) and secondary outcomes (*i.e.*, pain scores, patient satisfaction), comparisons between the treatment groups were performed using the Wilcoxon rank-sum test (otherwise known as the Mann–Whitney U test). For side effects (secondary outcomes) and other categorical variables, comparisons were made using the chi-square test. However, if there was an expected cell count of less than 5, then the Fisher exact test was utilized.

For pain medication and pain score data, differences between treatment groups were calculated along with 95% CI using the cendif command in Stata, based on the Hodges–Lehmann method and consideration of all pairwise differences between the two sets of observations. In addition, box plots were generated for pain scores, stratified by treatment group and time. As a sensitivity analysis, and to obtain an overall estimate of treatment effect on pain, mixed-effects models were fit (appendix 2).

Statistical significance was defined as a two-tailed $P < 0.05$ based on tests of superiority; no formal adjustment for multiple testing or interim looks was made. Statistical analyses were performed using Stata 16 (StataCorp LLC, USA).

Results

All 140 patients scheduled for elective totally endoscopic CABG (June 19, 2018, through August 31, 2020) were assessed for eligibility (fig. 2). Of the 140 patients, 51 did not meet inclusion criteria: coagulopathy (n = 13), body mass index greater than 35 kg/m^2 (n = 9), left ventricular ejection fraction less than 40% (n = 9), severe pulmonary disease (n = 6), renal dysfunction (n = 5), anticipated postoperative extubation due to case complexity (n = 5), previous cardiothoracic surgery (n = 2), anticipated CPB support (n = 1), or preoperative cardiac support (n = 1). Ten patients declined.

The remaining 79 patients were randomized to the morphine (n = 37) or placebo (n = 42) group and included in the final analysis. A per-protocol analysis was performed. There were no instances of a traumatic spinal procedure with return of blood *via* the spinal needle. Free return of clear cerebrospinal fluid was unattainable in three patients (two morphine, one placebo). These three failed spinal patients were included in preoperative data analysis only and excluded from intraoperative and primary/secondary outcomes analysis. In six patients (two morphine, four placebo), extubation was not possible during the intraoperative or immediate postoperative period. These patients were included in preoperative/intraoperative data analysis and excluded from primary/secondary outcomes analysis. One placebo patient received postoperative PCA morphine, yet the data were lost. This patient was only excluded from primary outcome analysis.

Baseline preoperative characteristics and intraoperative data are presented in tables 1 and 2, respectively. The two groups had similar preoperative characteristics and intraoperative anesthetic management. Time from intrathecal dose to administration of IV heparin was similar in both groups (morphine 3 h [2.8 to 4], placebo 3 h [2.6 to 3.8]). Fifty patients were targeted by surgeon/anesthesiologist for intraoperative extubation (22 [63%] morphine, 28 [68%] placebo; $P = 0.806$) and were successfully extubated. Of these 50 patients, significantly fewer morphine patients required fentanyl after extubation than placebo patients (6 [27%] *vs.* 19 [68%]; $P = 0.004$). Twenty-six patients were targeted for immediate postoperative extubation (13 [37%] morphine, 13 [32%] placebo). These patients were not extubated in the operating room for the following reasons: surgeon's concern for bleeding (eight morphine, seven placebo), hemodynamic instability (three morphine, three placebo), hypoxemia (one morphine), pulmonary edema (one morphine), and respiratory acidosis (three placebo). Of these 26 patients, immediate postoperative extubation was successful in 21 patients (11 [42%] morphine, 10 [38%] placebo), and median extubation time from ICU arrival was equivalent between groups (morphine 5 h [2.5 to 7], placebo 4.5 h [3.5 to 6.5]; $P = 0.834$). Six patients required overnight mechanical ventilation (two morphine, four placebo). Clinical reasons included hemodynamic instability (one morphine, two

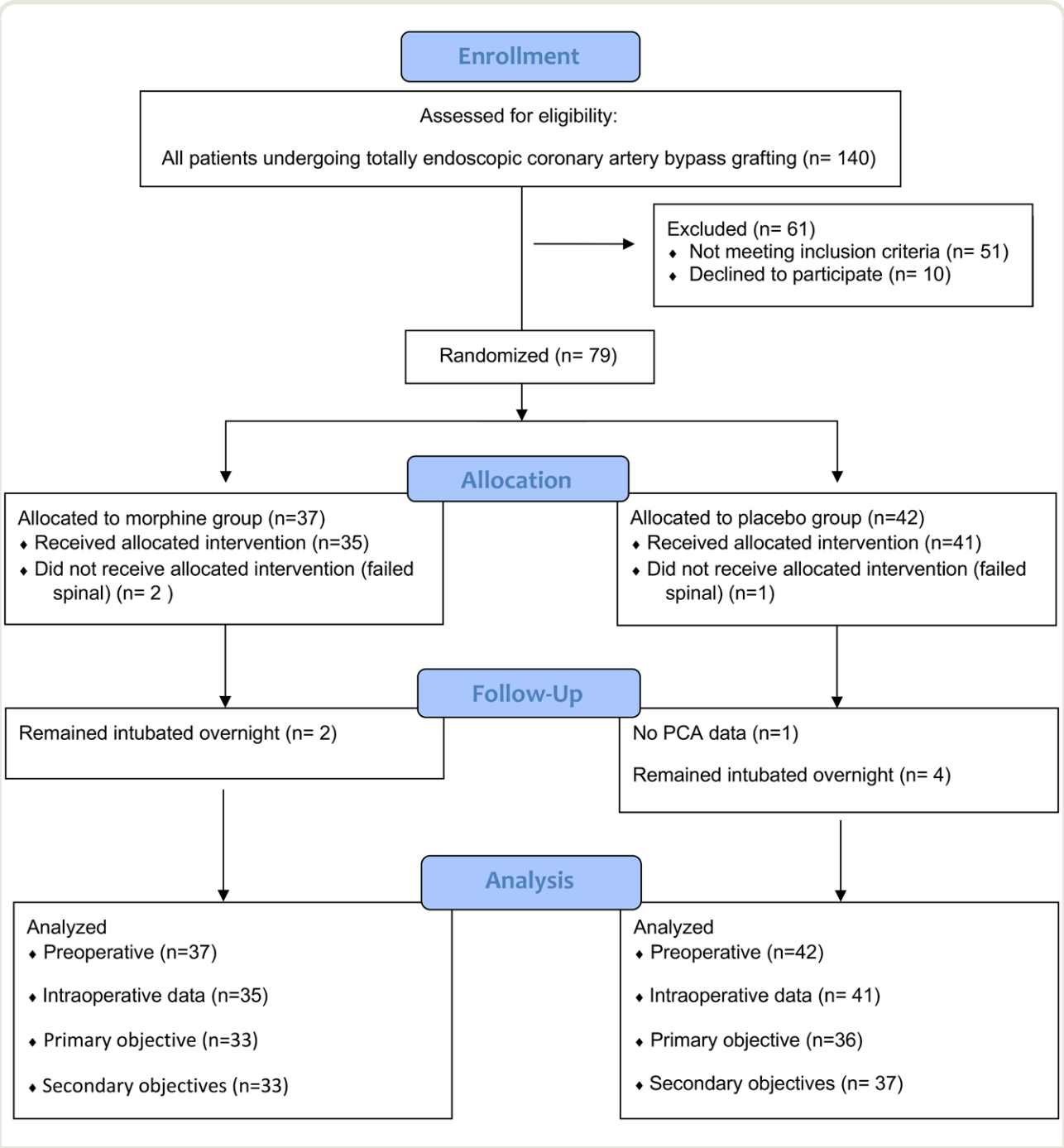

Fig 2. Consolidated standards of reporting trials diagram. PCA, patient-controlled analgesia.

placebo), pulmonary edema (one morphine), and respiratory acidosis (one placebo). One placebo patient underwent intraoperative extubation yet required immediate postoperative reintubation due to bleeding (extubated the next day).

Primary Outcome

Postoperative morphine requirements are presented in table 3. Of the 69 patients assessed, 23 received the IV fentanyl protocol (11 [16%] morphine, 12 [17%] placebo), and 46 received the IV morphine protocol (22 [32%] morphine, 24 [35%] placebo). Morphine patients required significantly less IV morphine PCA (26 mg [18 to 36] *vs.* 50 mg [37 to 77]; $P < 0.001$), significantly fewer patients required ketorolac (13 [39%] *vs.* 26 [72%]; $P = 0.006$), and significantly fewer median tramadol tablets were needed ($P = 0.04$). During surgical ward stay,

Table 1. Baseline Preoperative Characteristics

	Morphine (n = 37)	Placebo (n = 42)
Demographics		
Age, yr	67.3 ± 10.5	64.5 ± 10.0
Male sex	32 (86.5)	33 (78.6)
Weight, kg	85 ± 14	87 ± 14
Body mass index, kg/m^2	27.5 ± 3.3	28.6 ± 3.6
Medical history		
ASA physical status	3 (3–4)	3 (3–4)
Euroscore II	1.0 ± 0.5	1.0 ± 0.5
Ejection fraction, %	54.5 ± 9.3	55.8 ± 7.6
Hypertension	25 (67.6)	35 (83.3)
Hyperlipidemia	19 (51.4)	30 (71.4)
Diabetes		
Non–insulin-dependent	7 (18.9)	5 (11.9)
Insulin-dependent	2 (5.4)	2 (4.8)
OSA	3 (8.1)	4 (9.5)
COPD	2 (5.4)	3 (7.1)
Hypothyroidism	3 (8.1)	5 (11.9)
Serum creatinine, mg/dl	0.97 ± 0.21	1.02 ± 0.26
Medications		
β-Blocker	21 (56.8)	32 (76.2)
Calcium blocker	10 (27.0)	9 (21.4)
Angiotensin-converting enzyme inhibitor	9 (24.3)	15 (35.7)
Angiotensin II receptor blockers	4 (10.8)	11 (26.2)
Diuretics	4 (10.8)	13 (31.0)
Nitrates	9 (24.3)	9 (21.4)
Statins	31 (83.8)	38 (90.5)
Aspirin	28 (75.7)	31 (73.8)

The values are presented as mean ± SD, median (interquartile range, 25th to 75th percentile), or number of patients (%).

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

Table 2. Intraoperative Data

	Morphine (n = 35)	Placebo (n = 41)	*P* Value
Midazolam, mg	4 (2–5)	4 (4–5)	0.219
Intrathecal morphine, mcg	421.8 ± 69.5	—	
Sufentanil, mcg	40 (25-45)	40 (35–45)	0.194
Propofol, mg	70 (50–120)	100 (60–140)	0.187
Rocuronium, mg	190 (150–220)	170 (150–200)	0.431
Ketorolac*	10 (45.5)	20 (71.4)	0.063
Fentanyl*	6 (27.3)	19 (67.9)	0.004
Urine output, ml	200 (150–320)	245 (190–325)	0.158
Bypass grafts			0.942
1	13 (37.1)	17 (41.5)	
2	19 (54.3)	20 (48.8)	
3	3 (8.6)	4 (9.8)	
Surgery time, min	315 (235–366)	290 (238–346)	0.399

Data are median (interquartile range, 25th to 75th percentile), mean ± SD, or number of patients (%).

*n = 22 morphine, 28 placebo. This reflects patients targeted for intraoperative extubation.

significantly fewer morphine patients required oral analgesics when compared to placebo patients (15 [46%] *vs.* 25 [69%]; $P = 0.044$). Morphine patients required significantly fewer morphine equivalents during the initial 24 h (28 mg [16 to 46] *vs.* 59 mg [41 to 79]; $P < 0.001$), the second 24 h (0 mg [0 to 2] *vs.* 5 mg [0 to 6]; $P < 0.001$), and during the entire 48 h (28 mg [16 to 48] *vs.* 63 mg [43 to 84]; $P < 0.001$).

Secondary Outcomes

Pain scores, side effects, and patient satisfaction questionnaire results are presented in tables 4, 5, and 6, respectively. Pain scores at rest and cough were significantly lower in the morphine group (rest median, 0 to 2.5; cough median, 1.5 to 3) than in the placebo group (rest median, 4.5 to 8; cough median, 7 to 10; rest, $P < 0.001$ to 0.028; cough, $P < 0.001$ to 0.009; fig. 3). In sensitivity analyses, for both rest and cough, there was a statistically significant overall treatment effect (–4.1 [95% CI, –4.9 to –3.3], and –4.7 [95% CI, –5.5 to –3.9]), respectively with $P < 0.001$, based on 6 degrees of freedom tests from mixed-effects models including all timepoints (appendix 2).

While no patient in either group vomited, more morphine patients experienced mild nausea compared to placebo patients (12 [36%] *vs.* 3 [8%]; $P = 0.004$). All instances of nausea and/or pruritus were reported as mild and were treated with ondansetron and hydroxyzine, respectively. One placebo patient required straight catheterization after Foley catheter removal. There were no instances of prolonged intubation secondary to hypercarbia and/or escalation of respiratory support after extubation thought to be secondary to hypercarbia (respiratory depression) in either group.

Sixty-three patients completed the Revised American Pain Society Outcome Questionnaire (28 [85%] morphine, 35 [95%] placebo). Reasons for loss of data were early hospital discharge (two morphine, two placebo) and completed questionnaires being lost (three morphine). While overall satisfaction was high in both groups, results from the questionnaire support the analgesic benefits of intrathecal morphine. When compared to placebo patients, morphine patients had significantly lower "least pain" scores ($P = 0.007$) and significantly lower "worst pain" scores ($P = 0.002$), they spent significantly less "percent time in severe pain" ($P = 0.003$), and they reported significantly more "percentage pain relief in prior 24 h" ($P = 0.015$).

Overall, patients in both groups experienced a relatively uneventful postoperative course. Three patients developed new-onset atrial fibrillation (one morphine, two placebo), and one patient in each group exhibited postoperative respiratory insufficiency due to hypoxemia. There were no differences between groups regarding ICU length of stay (morphine median, 24 h [21 to 27] *vs.* placebo median, 24 h [22 to 27]; $P = 0.241$) or median hospital length of stay (morphine, 2 days [1.6 to 2] *vs.* placebo, 2 days [2 to 2]; $P = 0.833$).

Table 3. Primary Outcome: Postoperative Morphine Requirements

	Morphine (n = 33)	Placebo (n = 36)	Hodges–Lehman Estimator (95% CI)	*P* Value
Time to first analgesic, min	60 (27–144)	27.5 (12–76)	19 (–2 to 52)	0.061
Fentanyl, mcg*	150 (100–525)	375 (300–437.5)	–181 (–300 to 150)	0.554
Morphine (mg) PCA†	26 (18–36)	49.5 (37–77)	–24 (–38 to –12)	< 0.001
Ketorolac	13 (39.4)	26 (72.2)		0.006
Hydromorphone	0 (0)	3 (8.3)		0.240
Median amount, mg	—	0.4 (0.2–0.6)		—
Oral medications‡				
Hydrocodone	6 (18.2)	14 (38.9)		0.058
Median tablets	3 (2–5)	3.5 (2–4)		0.704
Oxycodone	4 (12.1)	8 (22.2)		0.269
Median tablets	2.5 (1.5–3)	2 (2–3)		> 0.999
Tramadol	9 (27.3)	18 (50)		0.053
Median tablets	1 (1–1)	2 (1–3)		0.040
Cumulative	15 (45.5)	25 (69.4)		0.044
Median tablets	2 (1–4)	4 (2–6)		0.122
Morphine equivalent, mg				
First 24 h	28 (16–46)	59 (41–79)	–28 (–40 to –18)	< 0.001
Second 24 h§	0 (0–2)	5 (0–6)	–3.3 (–5 to 0)	< 0.001
First 48 h	28 (16–48)	63 (43–83.8)	–31.5 (–44 to –20.3)	< 0.001

Data are median (interquartile range, 25th to 75th percentile) or number of patients (%) unless otherwise noted.

*Data represent number of patients enrolled before February 19, 2019, n = 11 morphine, 12 placebo. †Data represent number of patients enrolled on and after February 19, 2019, n = 22 morphine, 24 placebo. ‡Oral medications were prescribed after intensive care unit discharge until hospital discharge. §n = 54, 25 morphine, 29 placebo; 15 patients discharged within 24 h.

PCA, patient-controlled analgesia.

Table 4. Pain Scores

	Morphine	Placebo	Hodges–Lehman Estimator (95% CI)	*P* Value
Pain at rest				
1 h	2 (0–4)	8 (7–9)	–6 (–7 to –4)	< 0.001
2 h	1.5 (0–4)	7 (5–9)	–5 (–6 to –3)	< 0.001
6 h	2.5 (0–3)	7 (4–8)	–4 (–6 to –3)	< 0.001
12 h	1 (0–3)	5 (3–7)	–4 (–5 to –2)	< 0.001
24 h	0 (0–2)	5 (2–6)	–4 (–5 to –2)	< 0.001
48 h	0 (0–1.5)	4.5 (1–7)	–3 (–6 to 0)	0.028
Pain with cough				
1 h	3 (1–5)	10 (9–10)	–6 (–7 to –5)	< 0.001
2 h	3 (0–6)	9 (7–10)	–5 (–7 to –4)	< 0.001
6 h	3 (2–5)	9 (6–10)	–5 (–6 to –3)	< 0.001
12 h	3 (0–5)	7 (5–9)	–4 (–5 to –3)	< 0.001
24 h	2 (0–4)	7 (4–8)	–4 (–5 to –3)	< 0.001
48 h	1.5 (0–3.5)	7 (3–8)	–4 (–7 to –1)	0.009

Data are reported as median (interquartile range, 25th to 75th percentile) unless otherwise noted. *P* values are from Wilcoxon rank-sum tests; conclusions were the same based on appropriate contrasts from mixed-effects models.

Table 5. Opioid-related Side Effects

	Morphine (n = 33)	Placebo (n = 37)	*P* Value
Nausea	12 (36.4)	3 (8.1)	0.004
Vomiting	0 (0)	0 (0)	—
Pruritus	7 (21.2)	2 (5.4)	0.074
Urinary retention	0 (0)	1 (2.7)	> 0.999
Respiratory depression	0 (0)	0 (0)	—

Data are n (%).

Discussion

This randomized, placebo-controlled, double-blinded, clinical investigation indicates that intrathecal morphine provides significant analgesia for the initial 48 postoperative hours in patients undergoing robotic totally endoscopic CABG. Significant reductions in postoperative morphine consumption, postoperative pain scores (rest, cough), and subjective pain scores (Revised American Pain Society Outcome Questionnaire) were demonstrated with minimal side effects. Thus, the technique may prove useful in patients undergoing minimally invasive cardiac surgery in the current enhanced recovery after surgery era.

Over the last 70 yr, cardiac surgery has progressed from sternotomy and universal use of CPB to minimal exposure *via* small thoracic incisions and avoidance of CPB (table 7).[16] This shift is reflected in anesthetic technique, with early use of large-dose IV opioids and delayed extubation to current practices of minimal IV opioids and early extubation. The trend toward minimally invasive cardiac surgery, along with increased utilization of enhanced recovery after surgery protocols, has led to an explosion of reports of regional techniques in patients undergoing a wide range of cardiac

Table 6. Patient Satisfaction Questionnaire

Variable	Morphine (n = 28)	Placebo (n = 35)	*P* Value
Satisfied with pain treatment (0–10 scale)	9.5 (6.5–10)	9 (7–10)	0.722
Least pain in prior 24 h (0–10 scale)	2 (0–3)	3 (2–5)	0.007
Worst pain in prior 24 h (0–10 scale)	7 (5.5–8.5)	8 (8–10)	0.002
Percent time in severe pain (0–100 scale)	10 (0–40)	40 (20–70)	0.003
How much pain interfered with (0–10 scale)			
Activity in bed	4 (1–8)*	6 (5–8)	0.047
Activity out of bed	3 (2–5)*	5 (3–7)	0.211
Falling asleep	2 (0–7)*	3 (1–6)	0.762
Staying asleep	2 (0–6)*	5 (3–7)	0.017
How much pain caused (0–10 scale)			
Anxiety	3 (0–6.5)	3 (1–5)	0.618
Depression	0 (0–2.5)	0 (0–3)	0.759
Fright	0 (0–3.5)	0 (0–3)	0.966
Helplessness	0 (0–3.5)	1 (0–5)	0.269
How severe were symptoms of (0–10 scale)			
Nausea	0 (0–5.5)	1 (0–3)	> 0.999
Drowsiness	3 (1–6.5)	5 (1–6)	0.567
Itching	0 (0–2)*	0 (0–0)†	0.179
Dizziness	3 (0–6)*	0 (0–2)	0.020
Percentage pain relief in prior 24 h (0–100 scale)	70 (60–90)*	60 (30–80)	0.015

Data are median (interquartile range, 25th to 75th percentile) or n (%). Statistics are presented for relevant patient responses to select questions from the Revised American Pain Society Outcome Questionnaire.

n = 28 for morphine and 35 for placebo group, except where noted with

*(n = 27, 1 patient did not answer this question), and †(n = 34, 1 patient did not answer this question).

surgeries. Specific clinical advantages/disadvantages of each technique are beyond the scope of this manuscript yet have been recently summarized.[17–25] Advancements in ultrasound-guided techniques have led to an increased use of fascial plane blocks. Major unresolved issues regarding these techniques involve simplicity (easily performed in a busy clinical environment), reliability of postoperative analgesia, time period of analgesia produced (single shot *vs.* catheters), and side effect profile/safety.

There is tremendous interest in regional techniques as part of a multimodal pain strategy. An ideal regional approach to the cardiac surgical patient should take into consideration the myriad sources of pain, including tissue retraction, artery dissection, body positioning, chest tubes, incision, and inflammation from surgical trauma. Unique challenges are associated with regional techniques in minimally invasive cardiac surgery. Erector spinae and paravertebral blocks are limited by high failure rate, potential adverse events in the setting of heparinization (hematoma), hemodynamic effects (epidural spread/sympatholysis), short duration of analgesia, and reports of local anesthetic toxicity.[26–28] Fascial plane blocks have limited analgesic coverage, with beneficial analgesic effects limited to the upper anterolateral, lateral, and parasternal chest wall, respectively. In contrast, intrathecal morphine offers a simple, reliable, and safe modality of providing analgesia to multiple sources of pain in patients undergoing any type of minimally invasive cardiac surgery. Not without risk, postdural headache, failed spinal, and rare instances of spinal hematoma have been reported. In our clinical trial, besides three failed spinals, we did not observe any other issues associated with a neuraxial technique.

Application of intrathecal morphine during cardiac surgery was initially reported in 1980,[29] with subsequent small randomized controlled trials demonstrating decreased use of postoperative opioids and enhanced analgesia in patients receiving intrathecal morphine.[30] The first clinical trial investigating the potential benefits of intrathecal morphine in fast-track cardiac surgery in 1997 randomized 40 patients to receive either intrathecal morphine (10 mcg/kg) or intrathecal placebo before induction.[31] Time to extubation was significantly prolonged in patients who received intrathecal morphine compared to placebo controls, with postoperative IV morphine use equivalent between groups. A follow-up study also found that four patients receiving intrathecal morphine had prolonged respiratory depression.[32] The authors concluded that although intrathecal morphine can produce reliable postoperative analgesia, its use in the setting of fast-track cardiac surgery (*via* median sternotomy) may potentially delay tracheal extubation.[31,32] Given these findings with larger doses, our investigation used a dose of intrathecal morphine (5 mcg/kg) that would potentially enhance postoperative analgesia without impacting early extubation. Also consistent with other studies on pain relief in cardiac surgery, morphine equivalent was chosen as a primary outcome in our clinical trial.

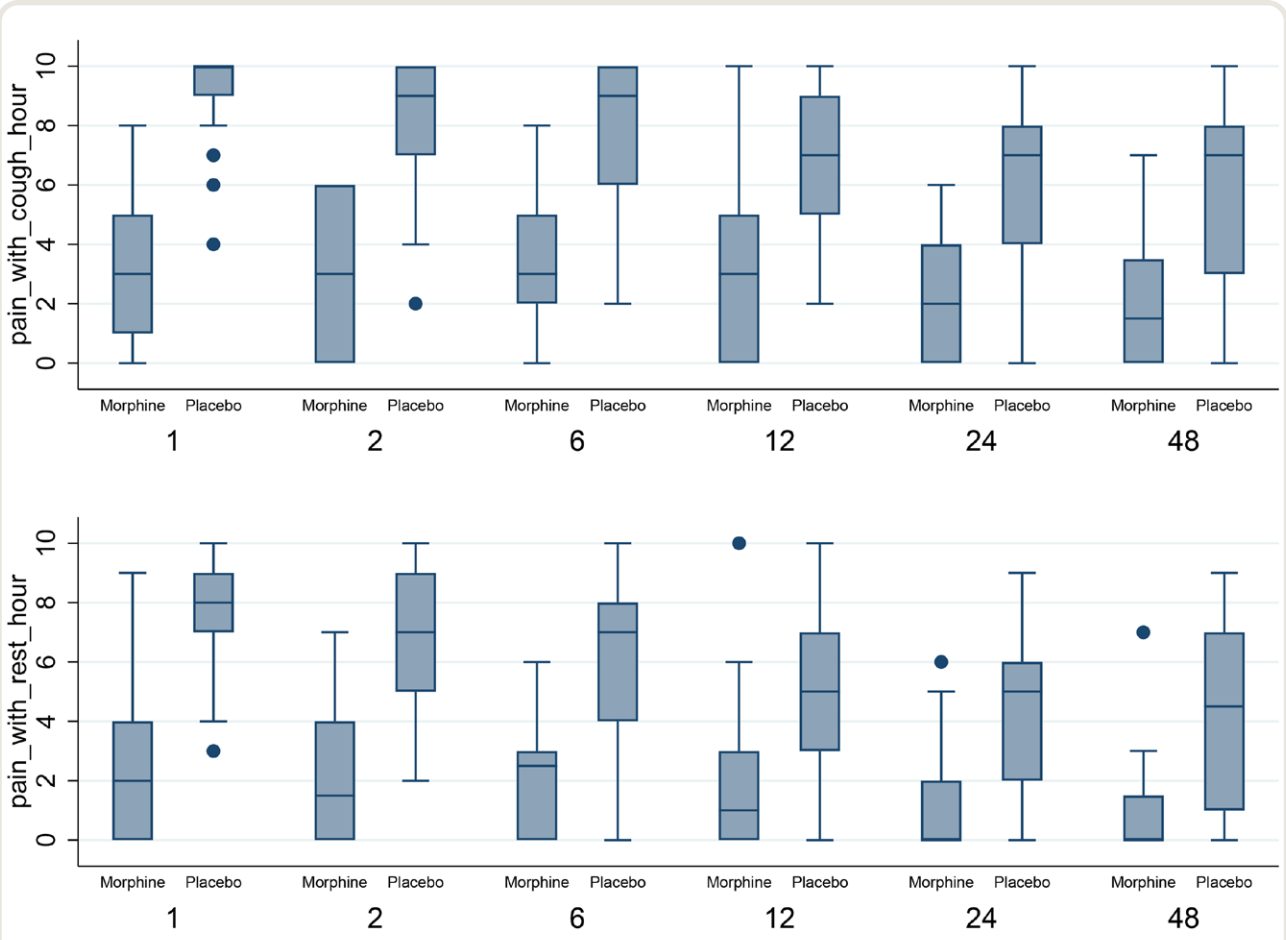

Fig. 3. The *box-plot* displays the median (*line within box*), 25th to 75th percentiles (*bottom to top edge of box*), and the 25th percentile –1.5 (interquartile range) to the 75th percentile +1.5 (interquartile range; *whiskers*) of pain scores at 1, 2, 6, 12, 24, and 48 h at rest and cough between the morphine and placebo groups. For both rest and cough, the overall treatment effect gave $P < 0.001$ (based on 6 degrees of freedom tests from mixed-effects models).

In the early 2000s, others continued to explore potential clinical benefits of intrathecal morphine in patients undergoing cardiac surgery, without reliable success. In 2009, three large reviews/meta-analyses focusing on use of intrathecal morphine in patients undergoing cardiac surgery concluded that this practice provides postoperative analgesia with only questionable potential clinical benefits (decreased extubation time, improved pulmonary function) and is associated with clinically important pruritus and potential respiratory depression.[33–35] One set of authors felt the technique should be abandoned.[35] The vast majority (if not all) of the clinical studies assessed by these three reviews/meta-analyses possess major methodologic design problems (small, retrospective, and others). However, two studies hint that intrathecal morphine

Table 7. Evolution of Cardiac Surgery and Anesthetic Technique

Era	Approach	Anesthetic Technique	Extubation Goal
1950s–1980s	Sternotomy, CPB	Large-dose IV morphine	Next postoperative day
1980s	Sternotomy, CPB	Large-dose IV fentanyl	Next postoperative day
1990s	Sternotomy, minithoracotomy, CPB, off-CPB	Small-dose IV fentanyl regional	Immediate postoperative period
2000s	Sternotomy, minithoracotomy, robotic ports, CPB, off-CPB	Regional IV "opioid-free"	In operating room Immediate postoperative period

CPB, cardiopulmonary bypass; IV, intravenous.

may be uniquely beneficial in patients undergoing minimally invasive cardiac surgery, yet one is small (22 patients) and retrospective,[36] and the other is not blinded,[37] limiting interpretation of the results. Based on this set of previously published work, intrathecal morphine in cardiac surgery has been relatively disregarded. However, the results of our study contribute to understanding the clinical efficacy and side-effect profile of intrathecal morphine in minimally invasive cardiac surgery and support its routine use in clinical practice.

The analgesic and adverse effects of intrathecal morphine are dose-dependent. Dose-response studies of intrathecal morphine in cardiac cases are limited. A large meta-analysis of randomized trials reported use of various doses of intrathecal morphine in cardiac surgery (0.5 mg to 4 mg, weight-based 1.5 mcg/kg to 10 mcg/kg).[38] Noncardiac surgery dose-response studies indicate that respiratory depression (increased $Paco_2$) can be significant with doses greater than 1 mg, with no additional analgesic benefit.[39,40] Our clinical trial indicates that low-dose intrathecal morphine resulted in significantly decreased pain scores for 48 h with rest and cough. Furthermore, when assessing the four clinically important opioid-related side effects of nausea/vomiting, pruritus, urinary retention, and respiratory depression,[41] only nausea was significantly increased by this dose.

How important is pain after cardiac surgery? While the quality of postoperative analgesia has never been directly linked to decreased morbidity/mortality,[42,43] it is clearly important in the current era of enhanced recovery after surgery and plays an important role in patient satisfaction.[7,8,44] Several pertinent clinical questions still remain for future investigational trials. The role of intrathecal morphine needs to be defined as it pertains to enhanced recovery after surgery, achieving an "opioid-free/sparing" postoperative recovery, and patient satisfaction. Future trials should determine optimal intrathecal morphine dose for clinically important analgesia without cumbersome effects of nausea and pruritus. This technique may aid in attaining an "opioid-sparing" hospital course, a recent concern/goal of anesthesiologists and patients.[45–48] Can intrathecal morphine in combination with fascial plane blocks provide an "opioid-sparing" postoperative recovery in minimally invasive cardiac surgery? Additionally, any purported hemodynamic benefits of intrathecal morphine in minimally invasive cardiac surgery are yet to be elucidated.

There are several limitations of our clinical trial. First, high-risk patients were excluded from enrollment. Patients with obstructive sleep apnea and morbid obesity were excluded due to the possibility of increased postoperative mechanical ventilation. A change in these exclusion criteria may potentially increase observed opioid-related respiratory depression. Second, the optimal dose of intrathecal morphine is unknown and not determined; however, based on previous studies, a dose was chosen to optimize analgesia with minimal side effects. Third, due to drug shortages, patients were transitioned from fentanyl (administered by nursing, possible less patient use) to PCA morphine (administered directly by the patient, possible increased use) during the study. This strategy was necessary; however, it may have decreased the observed difference between groups and effect size estimates. Fourth, because interim analysis indicated that the primary objective was met with fewer than anticipated patients, the study was stopped early by our IRB. Without consideration of multiplicity adjustments, there is potential for inflation of a type I error. Using an even stricter alpha adjustment of 0.002 (Haybittle–Peto) at interim analysis would still have led to the same conclusions about the primary outcome (morphine equivalent) and pain scores. Fifth, we excluded some randomized participants from the primary analysis, possibly introducing bias into the treatment effect estimates. Although our analysis is per-protocol, we conducted an analysis for the primary outcome using all available data, leading to the same conclusions. Finally, only short-term postoperative pain was assessed.

In conclusion, this clinical investigation reveals that 5 mcg/kg intrathecal morphine, when administered to patients before induction of anesthesia for totally endoscopic CABG, provides significant postoperative analgesia and decreased use of opioids for 48 h with minimal side effects. Thus, intrathecal morphine may prove useful in patients undergoing a wide variety of minimally invasive cardiac surgeries in the current enhanced recovery after surgery era.

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Competing Interests

Dr. Balkhy has received honoraria from Intuitive Surgical (Sunnyvale, California). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: rdhawan@dacc.uchicago.edu. Raw data available at: rdhawan@dacc.uchicago.edu.

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Appendix 1: Extubation Criteria

1. Awake and following commands
2. Hemodynamically stable
3. Adequate minute ventilation: tidal volume > 5 ml/kg, respiratory rate > 7 breaths per minute
4. End-tidal CO_2 < 55 mmHg
5. Full reversal of muscle relaxation: train of four ratio > 0.9
6. Oxygen saturation > 95%, fractional inspired oxygen tension 1.0
7. Normothermic: temperature > 35.5°C

Appendix 2: Mixed-effects Model for Pain Scores

For analysis of the pain scores, a mixed-effects regression model was fit. Patients were treated as a random effect to account for multiple observations per patient. Fixed effects covariates included treatment group (morphine *vs.* placebo) and time (1, 2, 6, 12, 24, and 48 h) indicators, and group by time interaction terms. Initially a linear model was fit, and results were confirmed using an ordinal logistic model. The parameterization of the model was of the general form

$$Y_{ij} = (b_1 + b_{1T}G)v_{i1} + (b_2 + b_{2T}G)\, v_{i2} + \ldots + (b_{48} + b_{48T}G)\, v_{i48} + a_i + e_{ij},$$

Table A2.1. Mixed-effects Model Treatment Effect on Pain

	At Rest		With Cough	
	Regression Coefficient	95% CI	Regression Coefficient	95% CI
v_1*	8.0	7.2 to 8.8	9.4	8.5 to 10
v_2*	7.0	6.2 to 7.8	8.3	7.5 to 9.1
v_6*	6.4	5.6 to 7.2	7.8	7.1 to 8.6
v_{12}*	5.2	4.4 to 6.0	7.0	6.2 to 7.7
v_{24}*	4.3	3.5 to 5.1	6.2	5.4 to 7.0
v_{48}*	4.2	3.1 to 5.3	6.0	5.0 to 7.1
Treatment group differences (morphine – placebo) at each timepoint				
$G \times v_1$	–5.5	–6.8 to –4.3	–6.0	–7.3 to –4.8
$G \times v_2$	–4.7	–6.0 to –3.5	–5.2	–6.4 to –4.0
$G \times v_6$	–4.3	–5.4 to –3.1	–4.4	–5.5 to –3.3
$G \times v_{12}$	–3.4	–4.5 to –2.3	–4.0	–5.1 to –2.9
$G \times v_{24}$	–3.2	–4.5 to –2.0	–4.1	–5.3 to –2.9
$G \times v_{48}$	–3.6	–5.5 to –1.7	–4.5	–6.2 to –2.7
Joint test (6 degrees of freedom) *P* value		< 0.001		< 0.001
Overall treatment effect†	–4.1	–4.9 to –3.3	–4.7	–5.5 to –3.9

*Estimates of the average pain level at a given timepoint in the placebo group.

†Calculated as the average of the treatment group differences at the six timepoints.

where Y_{ij} is the pain level for patient i at timepoint j, G is an indicator variable for treatment group (1 = morphine, 0 = placebo), v_{i1}, v_{i2}, …vi_{48} are indicator variables for the time at which the measurement was obtained, a_i is the random patient effect, and e_{ij} is residual error. Also, b_{1T}, b_{2T}, b_{6T}, b_{12T}, b_{24T}, and b_{48T} are treatment group differences at the six timepoints. An overall joint test ($b_{1T} = b_{2T} = b_{6T} = b_{12T} = b_{24T} = b_{48T} = 0$) based on 6 degrees of freedom was performed to test the significance of the treatment effect. In addition, an overall treatment effect was calculated as the average of the treatment group differences at the six timepoints. The results are provided in table A2.1.