

Study Title: Randomized, double blinded, placebo controlled trial comparing intrathecal morphine with placebo in patients undergoing robotic totally endoscopic beating heart coronary revascularization and intraoperative extubation (TECAB)

NCT #: 03241485

Protocol Version Date: 26JUN2019

PI: Richa Dhawan. MD MPH

MATERIALS AND METHODS

This clinical trial was approved by the University of Chicago Institutional Review Board (IRB) and was registered at Clinicaltrials.gov (NCT03241485) on August 7, 2017 prior to patient enrollment. This manuscript 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 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 (intravenous [IV] inotropes and/or vasoconstrictors/intraaortic 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/m²), 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.

Following 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}

Prior to study commencement, a study statistician created a computer generated randomization list (using simple randomization) to allocate study arm assignments in 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 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 morphine syringe. Ultimately, a three ml syringe (total volume one 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 monitors and achieving IV access, one 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 (Pajunk, Germany) needle was inserted via the L3-4 or L4-5 interspace (introducer-assisted) under sterile conditions. Upon free return of clear cerebrospinal fluid (CSF), the one 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 induced.

Intraoperative anesthetic technique was standardized in all patients. Induction consisted of IV midazolam (2-4 mg), sufentanil (0.5 mcg/kg), propofol (1 mg/kg), and rocuronium (0.6

mg/kg). Following intubation, inhaled desflurane was adjusted to maintain a Bispectral Index (BIS[®] system; Aspect Medical Systems, USA) value of 40-60 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, Bloomington, IN) or EZBlocker (Teleflex Life Sciences Ltd., Athlone, 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 normocarbida, FiO₂ 100%, and positive end-expiratory pressure 5 cm H₂O). Post-induction, 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 (Figure 1) and the Da Vinci[®] surgical system (Da Vinci, Intuitive Surgical, USA). The left and/or right internal thoracic artery served as conduits. Typically, IV heparin was administered (100-150 units/kg; activated clotting time goal 250 seconds) prior to distal anastomoses, which was ultimately reversed with IV protamine (1 mg/100 units 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. IV fentanyl was allowed if clinically indicated (pain) prior to transport to the intensive care unit (ICU).

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. 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 minutes) later (February 19, 2019 to August 31, 2020). The reason for this transition was 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 six 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 mg-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 was collected by research team members and nurses who were blinded to Group assignment. Preoperative data was 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 following ICU admission via a visual analog scoring (VAS) 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 catheterization after Foley catheter removal. Opioid-specific respiratory depression was defined as prolonged tracheal re-intubation secondary to hypercarbia (arterial blood gas analysis) and/or escalation of respiratory support following extubation thought to be secondary to hypercarbia.

Prior to hospital discharge, patients completed the Revised American Pain Society Outcome Questionnaire, which evaluates subjective experiences of pain following 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 (standard deviation 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 9/21/2020 the IRB chose to permanently close the study for enrollment because “the primary end point 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 \pm SD for normally distributed continuous variables, median (25th-75th percentile) for continuous variables with evidence of non-normality 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 chisquared test. However, if there was an expected cell count of <5 , then Fisher’s exact test was utilized.

For pain medication and pain score data, differences between treatment Groups were calculated along with 95% confidence intervals (CIs) 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, College Station, TX).