

Intravenous Methadone Versus Intrathecal
Morphine for Analgesia Following Cesarean
Delivery: a Randomized Clinical Trial

NCT06826742

10August2025

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Title: Intravenous methadone versus intrathecal morphine for analgesia following cesarean delivery: a randomized clinical trial

Objectives:

Specific Aims

Specific Aim 1: To determine if there is a difference in opioid requirements at 0-48 hours after scheduled cesarean delivery in patients receiving 150 mcg intrathecal morphine compared to 0.2 mg/kg (maximum 20 mg) intravenous methadone.

Specific Aim 2: To determine if there is a difference in pain scores, ObsQoR-10 scores, PGIC scores in patients receiving 150 mcg intrathecal morphine and 0.2 mg/kg intravenous methadone after scheduled cesarean delivery.

Specific Aim 3: To determine if there is a difference in opioid related side effects such as pruritis, respiratory depression, nausea, or sedation in patients receiving 150 mcg intrathecal morphine and 0.2 mg/kg intravenous methadone after scheduled cesarean delivery.

Hypothesis: We hypothesize that there would be a decrease in opioid requirement at 0-48 hours after scheduled cesarean delivery in patients receiving 0.2 mg/kg (maximum 20 mg) intravenous methadone compared to those that received 150 mcg intrathecal morphine.

Background:

After childbirth, increased postpartum pain is associated with negative outcomes including postpartum depression, breastfeeding difficulties, and chronic pain.¹⁻⁵ In addition, severe acute postpartum pain is associated with a 2.5-fold increased risk of persistent pain and a 3.0-fold increased risk of postpartum depression at 8 weeks postpartum compared to those with mild postpartum pain.⁶ The interplay amongst maternal pain, mood and functional outcomes and how these relate to newborn bonding and newborn outcomes is complex and demands further study.

Intrathecal morphine is considered by many to be the gold standard for post cesarean analgesia.⁷⁻⁹ Methadone is an alternative, long-lasting systemic opioid for postsurgical analgesia, which has been studied in various populations including pediatric spine, adult cardiac, and outpatient procedure patients.¹⁰⁻¹³ Methadone use has been reported in a retrospective study for cesarean

deliveries requiring general anesthesia, which showed lower pain scores and less opioid requirement in those who received IV methadone supplementation.¹⁴ Notably, methadone's effect of N-methyl-d-aspartate (NMDA) receptor antagonism could decrease hyperalgesia and acute opioid tolerance, thus aiding postsurgical opioid-sparing strategies.^{10, 15} Further, methadone could help boost mood and promote descending inhibitory pathways by preventing serotonin and norepinephrine reuptake.^{16, 17}

An additional consideration is the impact of methadone on the breast-feeding neonate. Potential adverse effects for a neonate could include lethargy and respiratory depression. However, methadone has been well studied in lactating patients with over 60 studies referenced in the LactMed database.¹⁸ Studies involving women receiving oral methadone treatment for substance use disorder have shown that methadone levels in breastmilk are low as are infant plasma concentrations.¹⁹⁻²¹

Methods

Design: Prospective, randomized, two-arm, superiority pilot study comparing the opioid requirements in patients receiving IV methadone versus intrathecal morphine after scheduled cesarean delivery.

Subject Selection

Inclusion:

- English-speaking
- Age over 18 years old
- Scheduled cesarean delivery

Exclusion:

- Any contraindication to the administration of a spinal technique for anesthesia
- History of intolerance or adverse reaction to opioid medications
- History of chronic pain, opioid use >30 OME/day, or substance use disorder
- History of obstructive sleep apnea, chronic obstructive pulmonary disease, or respiratory compromise (SpO₂ <92% on room air, or has a pre-existing oxygen requirement)
- History of liver or kidney failure
- Diagnosis of pre-eclampsia with current pregnancy
- Depression requiring more than one medication
- Planned use of CSE technique
- BMI >50.0 kg/m²
- ASA status IV, V
- No prior history of an ECG demonstrating QTc > 440ms
- Surgical complication requiring conversion to general anesthesia

Subjects will consist of patients who present for scheduled cesarean delivery at the Family Birthing Center at Mayo Clinic, Rochester Methodist Campus. Subjects will be approached following verbal communication and approval by their obstetric provider. Recruitment will ideally occur either at the patient's last obstetric visit prior to planned delivery or by telephone call 2-7 days prior to her cesarean delivery. Recruitment may also occur on the morning of the scheduled cesarean delivery in select cases. Only licensed physician investigators will recruit subjects. No remuneration will be provided. All efforts will be made to enroll participants

regardless of ethnic heritage. No passive recruitment methods (newspapers, advertisements, or flyers) will be used.

Study Procedures

Intervention (two arms): Arm 1: Standardized spinal anesthesia without intrathecal morphine (intrathecal 1.6-2 mL 0.75% bupivacaine + dextrose, 15 mcg fentanyl) and intravenous methadone (0.2mg/kg total body weight up to max dose of 20 mg, with saline added to make total volume 2 mL,); Arm 2: Standardized spinal anesthesia with intrathecal morphine 150 micrograms and no methadone (2cc dose of IV normal saline) (Arm 2). The IV methadone or IV saline will be administered after cord clamping and administration of uterotonics with the dose of medication divided into 4 equal aliquots each administered 5 minutes apart. If maternal heart rate is <50 bpm, glycopyrrolate 0.2mg will be administered and subsequent methadone aliquots will be resumed once heart rate increases to >50 bpm. Bradycardia event will be documented in the data sheet. Randomization will be electronic. Randomization, spinal tray preparation and intravenous study drug preparation will be performed by a study team member who will neither be caring for the patient intraoperatively nor performing any of the outcome assessments. All patients will receive 4 mg of ondansetron at time of spinal placement and 4 mg dexamethasone after delivery of the baby. All patients will receive standardized postoperative multimodal analgesia (scheduled 1,000 mg of acetaminophen orally every 6 hours and 15 mg of ketorolac intravenously every 6 hours for three doses, which is then replaced with 600 mg of ibuprofen orally; oral oxycodone 5 mg as needed for NRS pain scores 4-6 and 10 mg for pain scores 7-10, scheduled acetaminophen, scheduled ketorolac/ibuprofen, and prn oxycodone). This allows for standard monitoring of respiratory rate, oxygenation, and sedation with appropriate treatment as needed. Postoperative nausea and pruritus will be treated as needed by current protocol. For this pilot study, we will aim for 15 evaluable patients in each arm (may need to enroll up to 50 patients in order to account for drop-out).

Data Collection: All data will be collected prospectively by patient interview at 12, 24, 36, and 48 hours after spinal administration (see data collection sheet). At each time point, patients will rate the following:

1. ObsQoR10
2. NRS score for pain (0-10) at rest
3. NRS score for movement-evoked pain (0-10) with provoking maneuvers such as cough, inspiration/expiration, sitting up, knee flexion, hip flexion, rolling over in bed, walking
4. Highest pain NRS (0-10) in previous 12 hours
6. Pruritus – 0 = none, 1 = mild, 2 = moderate, 3 = severe
7. Patient Global Impression of Change (PGIC)
8. Sedation score (Richmond Agitation Sedation Scale)
9. Any instances of respiratory hypopnea documented by nurse during assessment
10. Any intraoperative or nurse-verified instances of SpO2 less than 90% and less than 80%
11. Any instance bradycardia < 20% baseline (intra-operative after methadone administration and post-operative); need for glycopyrrolate or atropine (after methadone administration)
12. QBL

13. Supplemental oxygen requirement, respiratory rate (clinician-reported, not chart data)
14. Questions asked only at 12-hours postpartum: Did you experience pain during cesarean delivery? If yes, how would you rate your pain experienced during cesarean delivery? (0 is no pain and 10 being the worst pain imaginable). How satisfied are you with your anesthetic care on a scale of 1 to 10, 1 being the least satisfied and 10 being the most satisfied?
15. Questions asked only at 48-hours postpartum: How satisfied are you with your pain relief on a scale of 1 to 10, 1 being the least satisfied and 10 being the most satisfied?

Seven days post-delivery, patients will be contacted by text message to assess:

1. Current pain score at rest
2. Current pain score with standing up
3. Worst pain score in past 24 hours
4. Number of opioids prescribed
5. Number of opioids remaining
6. ObsQoR10
7. PHQ-9 Score

Other data collected from patient electronic records will include:

- 1) Total opioid consumption at 24 and 48 hours of intrathecal opiate or IV methadone administration
- 2) Total non-opioid analgesic consumption at 24 and 48 hours of intrathecal opiate administration
- 3) Medical treatment(s) for nausea or pruritus at 24 and 48 hours of intrathecal opioid administration
- 4) Maternal demographics and fetal characteristics (birthweight, Apgar scores)
- 5) Maternal need for post-partum rapid response team activation
- 6) Maternal and neonatal length of inpatient hospital stay

Primary Outcome: Total opioid consumption at 24-48 hours after delivery in groups as defined above.

Secondary Outcomes: Postpartum OB QoRs; total opioid consumption at 0-24 hours and 0-48 hours; NRS pain score at rest, with movement, and worst NRS pain score in prior 12 hours each at 12 hours, 24 hours, 36 hours, 48 hours; opioid-associated side effects including nausea, pruritus, sedation, hypopnea, hypoxia at each 0-24 and 24-48 hours. Rapid response team activation at 0-48 hours post-partum. PGIC scale. Opioid consumption at one-week post-discharge. Infant heart rate and respiratory rate will be assessed every 4 hours for first 24 hours and every 8 hours from 24-48 hours after delivery per nursing protocol.

Early end points:

- 1) Change in fetal or maternal health mandating the use of other anesthetic techniques
- 2) Inability to perform the spinal technique
- 3) Withdrawal of subject consent at any time

- 4) Surgical complications resulting in the need for additional surgical procedures

Subject Costs:

There will be no additional costs to the patient due to participation in this study. The costs of routine labor and delivery analgesia and anesthetic care will be the responsibility of the patient and their insurance provider.

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