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1 Pharmacology CE credit.*

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THE EFFECT OF INTRATHECAL MORPHINE DOSE ON OUTCOMES AFTER ELECTIVE CESAREAN DELIVERY: A META-ANALYSIS

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Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B

Abstract

Purpose The purpose of this study was to compare differences in time to first analgesic request; pain; and rates of pruritus, nausea, and vomiting in patients who received either low-dose (Low Dose: 50-100 µg) or high-dose (High Dose: >100-250 µg) spinal morphine for postoperative analgesia after cesarean delivery.

Background Spinal morphine is the most widely used analgesic after cesarean delivery because of its prolonged duration of action. The quality and duration of analgesia varies with the dose administered. Unfortunately, the incidence of side effects such as pruritus, nausea, vomiting, and respiratory depression increase as the dose increases. In one survey, 87% of anesthesia providers reported they administer between 50-200 µg of spinal morphine, with the most common dose being 200 µg. The optimal dose that provides extended analgesia with a favorable side effect profile is unclear. This meta-analysis sought to compare outcomes from studies in which either a Low Dose or High Dose of spinal morphine was administered for postoperative analgesia after cesarean delivery.

Methodology This was a systematic review and meta-analysis. The investigators first conducted a literature review to identify randomized controlled trials of women who were not in labor undergoing elective cesarean delivery with spinal anesthesia. Low dose spinal morphine (50-100 µg) was compared to High dose morphine (>100-250 µg). Studies were excluded if they combined different opioids with morphine (e.g., fentanyl). Outcomes examined included:

- time to first analgesic request
- pain scores at 12 and 24 hours
- morphine consumption
- maternal side effects

Maternal side effects included pruritus, severe pruritus, nausea, vomiting, and APGAR scores in neonates. Statistical analysis was appropriate. A P < 0.05 was considered significant.

Result There were 11 studies included in the analysis with 247 patients in the Low Dose group and 233 in the High Dose group. No evidence of publication bias was found. In 6 of 11 studies, multimodal analgesia was used. In four studies patients received nonsteroidal anti-inflammatory drugs (NSAIDs), and in two studies patients received NSAIDs and acetaminophen. The regimens used (dosing as needed or at intervals around the clock) and timing (intraoperative only and/or postoperative) varied across studies.
Patients who received High Dose spinal morphine had significantly longer time to first analgesic request (4.5 hours; \( P = 0.0008 \)). In the Low Dose group the mean time to first analgesic request ranged from 9.7 to 26.6 hours compared to 13.8 to 39.5 hours in the High Dose group. No differences were found in pain scores at either 12 hours or 24 hours. Total morphine consumption was similar.

The incidence of pruritus was significantly lower in the Low Dose group (47\% vs. 69\%; \( P = 0.0001 \)). The incidence of severe pruritus was also significantly lower in the Low Dose group (\( P = 0.0006 \)). Between 6 and 7 patients would need to receive High Dose spinal morphine for 1 additional patient to experience either pruritus or severe pruritus (\( P = 0.02 \)). The rate of nausea and vomiting was significantly lower in the Low Dose group, about half as likely (\( P = 0.002 \)). No differences were found in neonatal APGAR scores between the two groups. No patients experienced respiratory depression.

**Conclusion**

High dose spinal morphine (>100 to 250 µg) provided on average 4.5 hours longer time to first analgesic request compared to lower doses (50 to 100 µg). However, high doses of spinal morphine were associated with higher rates of side effects (pruritus and nausea and vomiting). Anesthesia providers should consider these results when deciding which dose to administer.

**Comment**

The results of this study are useful to anesthesia providers because they can help inform decisions about the dose of spinal morphine to use for women undergoing cesarean delivery. If patients are most concerned about postoperative pain, consider a high dose, and if patients are worried about side effects, consider giving a low dose of spinal morphine. Additionally, consider administering around the clock or as needed NSAIDs (i.e., ketorolac) and/or acetaminophen, if there are no contraindications. IV acetaminophen is a nice option to consider, but its high cost may be prohibitive. I usually will only order IV acetaminophen if the patient has a history of chronic pain or is having breakthrough pain that is unrelieved by as needed pain medications. Also, do not forget to order medications to treat side effects (e.g., Nubain, Benadryl).

**Dennis Spence, PhD, CRNA**

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
PHARMACOLOGY

THE IMPACT OF RESIDUAL NEUROMUSCULAR BLOCKADE, OVERSEDATION, AND HYPOTHERMIA ON ADVERSE RESPIRATORY EVENTS IN A POSTANESTHETIC CARE UNIT: A PROSPECTIVE STUDY OF PREVALENCE, PREDICTORS, AND OUTCOMES

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Stewart PA, Liang SS, Huang ML, Bilgin AB, Li QS, Kim D, Phillips S

Abstract

Purpose The purpose of this study was to identify predictors and prevalence of residual neuromuscular blockade and adverse respiratory events.

Background The prevalence of residual neuromuscular blockade from nondepolarizing neuromuscular blocking drugs ranges from 30% to 60%. Residual block is associated with an increased risk of adverse respiratory events, such as upper airway obstruction, hypoxemia, and increased risk of aspiration. Residual block is defined as a train-of-four ratio (TOF-r) <0.90 using mechanomyography or electromyography. Unfortunately, detection of residual block in the post anesthesia care unit is difficult because quantitative monitors are rarely used. Furthermore, decreased level of consciousness and deep extubation in the operating room may contribute to adverse respiratory events making it difficult to determine the effect residual block has on adverse respiratory events.

Methodology This was a prospective cohort study of adult patients who required nondepolarizing neuromuscular blockade for surgery at a single institution in Sydney, Australia. Patients were excluded if they had neuromuscular disease or the surgical procedure prevented monitoring the TOF-r.

Data was collected on weekdays from 8 am to 8 pm. Within 5 minutes of admission to the PACU a TOFr monitor was used to evaluate the patient for residual block (TOFr <0.90). If the TOFr was <0.90, then the TOFr was checked every 15 minutes until the TOFr was >0.90.

Within 15 minutes of admission to the PACU, trained nursing staff recorded adverse respiratory events using the modified Murphy’s Criteria:

- upper airway obstruction
- mild-moderate hypoxemia (SpO2 90-93% on 6 l/min face mask O2)
- severe hypoxemia (SpO2 <90% on 6 l/min face mask O2)
- impending respiratory distress (e.g. RR >20)
- inability to breathe deeply on command
- complaint of respiratory or airway muscle weakness
- required assisted ventilation
- evidence or suspicion of aspiration

The investigators used multivariable logistic regression to identify predictors of residual block and adverse respiratory events. If a patient experienced one or more of the adverse respiratory events this was counted as an “event.” A P < 0.05 was considered significant.

Result There were 599 patients included who were treated by 81 different anesthesiologists. Patient average age was 57 years. Overall, 24% of patients had some form of neuromuscular monitoring.
intraoperatively. In all, 80% received neostigmine at the end of surgery.

Thirty-one percent (31%) of patients had a TOFr <0.90 in the PACU (Figure 1). The TOFr ranged from 0.14 to 1.0, with a median of 0.96. The median time to recover to a TOFr > 0.90 was 15 minutes (interquartile range = 15-30 minutes).

Predictors of residual block (TOFr <0.90) included:
- age
- procedure type
- surgical duration <90 minutes

For every 10-year increase in age, the risk of residual block increased 1.17 times. A lower risk of residual block was found in patients undergoing laparoscopic; orthopedic/spine; ear, nose and throat; urologic; or gynecologic procedures. Patients undergoing surgeries ≥90 minutes were at lower risk for experiencing residual block (RR = 0.59) compared to surgeries <90 minutes.

The rate of adverse respiratory events was 16% (n = 97). Twenty-five patients (26%) experienced multiple adverse respiratory events. The most common adverse respiratory events were:
- upper airway obstruction (78%)
- respiratory distress (12%)
- complaint of respiratory or airway muscle weakness (10%)
- inability to deep breathe (10%)
- severe hypoxemia (9%)
- assisted ventilation (3%)
- pulmonary aspiration (1%)

Twenty-one percent (21%) of patients with residual block experienced an adverse respiratory event, compared to 14% of patients who did not have residual block on admission to the PACU (Figure 2).

Predictors of adverse respiratory events (TOFr < 0.90) were core temperature and level of consciousness. For every 1°C decrease in core body temperature, there was a 43% increased risk of an adverse respiratory event. Compared to patients who were alert and awake, those that were unarousable/unconscious had a 4.76 times greater risk of experiencing an adverse respiratory event.

**Conclusion** At this institution the prevalence of residual block was over 30%. Older age, open abdominal surgery, and surgical duration <90 minutes

![Figure 1. Residual Neuromuscular Blockade by TOFr](image)
were associated with residual neuromuscular block. Hypothermia and decreased level of consciousness were associated with adverse respiratory events. Ensuring the patient is actively warmed, fully awake and responsive, and fully reversed prior to extubation may reduce adverse respiratory events.

**Comment**

It is surprising given the increased emphasis on the adverse events associated with residual neuromuscular blockade that we are still seeing anesthesia providers not consistently monitoring neuromuscular function with a nerve stimulator. In this study, only 24% of patients had a neuromuscular function monitor used intraoperatively. To me this is somewhat concerning. How can you titrate your reversal agent if you do not know your train-of-four response? Too much neostigmine can actually worsen residual block. I guess they were just going by the clock.

One of the points the investigators made in their discussion was that a majority of their anesthesia providers performed deep extubations. This explains why level of consciousness was a predictor of adverse respiratory events. This is a major bias to the study and probably explains why they did not find residual neuromuscular blockade to be significantly associated with adverse respiratory events. Fortunately, most of the events were not serious; most patients needed a jaw thrust or chin lift for airway obstruction. With a larger sample size the investigators may have found residual block to be a significant predictor of adverse respiratory events.

How can you use these results? Always use a neuromuscular monitor to guide your administration of neuromuscular blocking agents and reversal, and whenever possible use a quantitative monitor (consider getting your facility to purchase some). Be aware of the risks associated with deep extubation, especially in patients with obesity or sleep apnea, and make sure your PACU nurses are well trained to manage airway obstructions.

**Dennis Spence, PhD, CRNA**

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Pharmacology

Prevention of Spinal Anesthesia-Induced Hypotension During Cesarean Delivery by 5-Hydroxytryptamine-3 Receptor Antagonists: A Systematic Review and Meta-Analysis and Meta-Regression

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Heesan M, Klimek M, Hoeks SE, Rossaint R

Abstract

Purpose The purpose of this study was to conduct a systematic review and meta-analysis to determine the effect 5-hydroxytryptamine3 (5-HT3) receptor antagonists have on preventing spinal-induced hypotension.

Background Hypotension is common after spinal anesthesia. The mechanism leading to hypotension is sympatholysis causing a decrease in systemic vascular resistance. Another cause is the triggering of the Bezold-Jarisch reflex, which is activated by decreased venous return that triggers reflex vasodilation, bradycardia, and hypotension. 5-hydroxytryptamine3 receptor antagonists have been found to block the Bezold-Jarisch reflex in animal models; however, studies in humans are inconclusive.

Methodology The investigators used appropriate search terms and databases to identify randomized, placebo-controlled trials studying the preventative effects of 5-HT3 receptor antagonists on spinal-induced hypotension. Results were synthesized and meta-analysis techniques were used to analyze the results. Meta-regression was used to determine if there was a dose-response effect for ondansetron on spinal-induced hypotension.

Result The investigators identified 17 trials on 1,604 patients. Nine studies were in non-obstetric and eight studies were in obstetric patients. Including obstetric and non-obstetric patients, 5-HT3 receptor antagonists significantly reduced the rate of spinal-induced hypotension (RR = 0.54; number needed to treat = 6.3). In obstetric studies the 5-HT3 receptor antagonists reduced the risk of hypotension moderately (RR = 0.52, 95% CI 0.30 to 0.88; NNT = 4) But in non-obstetric patients 5-HT3 antagonists on bradycardia and hypotension were not statistically significant.

The most frequently studied drug was ondansetron 2 mg to 12 mg in 12 of the trials. In those trials, ondansetron reduced the risk of spinal-induced hypotension. However, in non-obstetric studies ondansetron did not reduce the risk of hypotension after spinal anesthesia. When studies in non-obstetric patients using only 6-12 mg ondansetron were included, a significant reduction in spinal-induced hypotension was found (RR = 0.23). However, a sensitivity analysis, which included only those studies whose primary outcomes were hypotension, found 5-HT3 receptor antagonists did not reduce the risk of spinal-induced hypotension in non-obstetric patients.
although it did significantly reduce the risk in obstetric study patients (RR = 0.52).

The rate of hypotension was reduced as the dose of ondansetron increased during non-obstetric surgeries (P = 0.04). No dose-response effect was found in obstetric studies.

Analysis of all studies suggested the presence of publication bias. All studies had high levels of heterogeneity, which suggests wide variation in study methodology (i.e., different definitions of hypotension, timing of ondansetron administration).

Conclusion 5-HT₃ receptor antagonists decreased the incidence of spinal-induced hypotension during cesarean delivery. However, in non-obstetric studies, only doses ranging from 6-12 mg were associated with a significant effect on reducing hypotension.

Comment Spinal-induced hypotension is very common during cesarean delivery. This study found that 5-HT₃ receptor antagonists, most commonly ondansetron, reduced the rate of hypotension after spinal anesthesia. An added benefit to this treatment is that prophylactic administration of ondansetron may also help reduce nausea and vomiting after cesarean delivery. I recommend you consider administering preoperative ondansetron in cesarean delivery patients. To be efficient, you might consider adding it to your standard preoperative order sets.

Dennis Spence, PhD, CRNA

Note: 5-hydroxytryptamine is also known by the name serotonin.

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