Published in final edited form as:

Reg Anesth Pain Med. 2017 ; 42(5): 669–673. doi:10.1097/AAP.0000000000000642.

The Effect of Ondansetron on Acute Opioid Tolerance in Patients Receiving Intrathecal Opioids Prior to Cesarean Delivery

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Abstract

Background—Multiple animal studies suggest that ondansetron ameliorates opioid-induced hyperalgesia and tolerance. In this study, we aimed to determine if the administration of ondansetron prior to spinal anesthesia would have an effect on intrathecal opioid-induced acute opioid tolerance, postoperative pain, and analgesic requirements in patients undergoing cesarean delivery with spinal anesthesia.

Methods—Eighty-six patients undergoing elective cesarean delivery were recruited and randomly allocated to receive either 8 mg intravenous ondansetron (n=44) or placebo (n=42) in a prospective, double-blind design. All patients received spinal anesthesia consisting of 15 mg bupivacaine, 20 µg of fentanyl, and 100 µg of preservative-free morphine. We used linear mixed-effects models to assess the difference in pain and opioid consumption in the first 24 hours after surgery between the 2 groups.

Results—No differences between the 2 groups were found in age, BMI, ASA scores, duration of surgery, or sensory and motor block characteristics. There was no difference between the 2 groups in postoperative pain scores ($P=0.95$) or opioid consumption ($P=0.68$).

Conclusions—In patients undergoing cesarean section under spinal anesthesia with intrathecal opioids, the administration of ondansetron prior to spinal anesthesia did not significantly affect postoperative pain scores or opioid consumption. Thus, the administration of ondansetron did not have an effect on acute opioid tolerance in our study.

Keywords

Acute opioid tolerance; 5HT3 receptors; Ondansetron

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Work Attributed to:

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Prior Presentation: This work was presented at the 45th Society of Obstetric Anesthesia and Perinatology Colorado Springs as a poster.

Conflict of Interest: The authors declare no conflict of interest.

Background

Opioids are commonly used as an adjunct to local anesthetics in subarachnoid block for cesarean delivery.¹ The addition of intrathecal fentanyl to subarachnoid local anesthetic has several advantages, including enhanced quality of intra-operative analgesia, prolonged duration of sensory block and delayed onset of postoperative pain without increasing significant maternal and fetal side effects.²⁻⁴ However, recently concern has been raised regarding development of acute opioid tolerance (AOT) and opioid-induced hyperalgesia (OIH), even when opioids are used within clinical accepted doses.⁵⁻⁷ While acute tolerance can be overcome by increasing the dosage, hyperalgesia is minimized by reducing or eliminating the opioid.⁸

The mechanism of acute opioid tolerance is not clearly understood and is likely to involve serotonergic pathways.⁹ As an example, the 5-hydroxy tryptamine type 3 (5-HT₃) receptor is now recognized as a target for treating opioid dependence.¹⁰ Recent genetic studies suggest that the 5-HT₃ receptor has a role in the development of opioid tolerance^{11,12}. Liang et al, found the 5-HT₃ receptor to modulate opioid-induced hyperalgesia and tolerance in mice.⁹ In that same study, systemic or intrathecal administration of ondansetron significantly prevented and reversed opioid-induced hyperalgesia and tolerance. Roychoudhury et al. found that repeated administration of ondansetron attenuated the development of morphine dependence in a murine model.¹³ Chu et al. demonstrated a reduction in naloxone-precipitated opioid withdrawal symptoms in mice and humans receiving ondansetron as compared to placebo.¹⁰

The effects of ondansetron on acute opioid induced tolerance in humans have not been examined. The purpose of this study was to determine if administration of intravenous ondansetron would attenuate intrathecal opioid-induced acute opioid tolerance by decreasing postoperative pain scores and analgesic requirements in patients undergoing cesarean delivery with spinal anesthesia. We hypothesize that patients receiving intravenous ondansetron prior to cesarean section will require less opioids and have a better pain scores postoperatively compared to those who did not receive ondansetron.

Methods

This is a secondary analysis from a previously published randomized controlled trial, in which we examined the effect of ondansetron on hemodynamic changes in patient undergoing elective cesarean section under spinal anesthesia.¹⁴ The study was approved by the University of Virginia institutional review board (IRB –HSR # 14583), and was registered at clinicaltrials.gov (NCT 01414777). In this study, we tested the hypothesis that ondansetron may prevent acute opioid induced tolerance to intrathecal opioids in patients undergoing cesarean delivery under spinal anesthesia.

Enrollment

Patients who presented for elective cesarean delivery at our institution between September 2010 and December 2012 were approached to participate in a double blind, randomized, placebo-controlled trial assessing the effect of intravenous ondansetron on hemodynamic

parameters. Exclusion criteria were diabetes, chronic hypertension, gestational hypertension, preeclampsia, cardiac disease, long QT syndrome, and any known contraindications to neuraxial anesthesia. After review of patients charts, those receiving opioid prenatally or dexamethasone intraoperatively were also excluded.

Randomization

The pharmacist was unblinded and prepared the syringes for all our study patients. Patients were randomized to 2 groups using Research Randomizer (www.researchrandomizer.org). Patients were allocated to each group using opaque sealed envelopes that were opened just before the surgery. All research team members were blinded. After randomization, age, weight, height, body mass index (BMI), and gestational age were recorded.

Study Protocol

An intravenous cannula was inserted, and all patients received aspiration prophylaxis (oral sodium citrate 30 mL, IV famotidine 20 mg, and IV metoclopramide 10 mg) preoperatively. On arrival to the operating room, ASA standard monitors were attached and initial vital signs (noninvasive blood pressure, HR, and SpO₂) were obtained. While in the sitting position, the study drug was administered over a period of 5 minutes. Group A, the ondansetron group, received 8 mg IV ondansetron diluted to 10 mL with saline before administration of the subarachnoid local anesthetic, whereas group B, the placebo group, received 10 mL of saline intravenously. Lumbar puncture was then performed using sterile technique, with a 24-gauge pencil-point needle at L4-L5 or L3-L4 level. A mixture of 15 mg of 0.75% bupivacaine, 20 µg of fentanyl, and 100 µg of preservative-free morphine was administered after confirmation of free flow of cerebrospinal fluid. Patients were then placed in the recumbent position with 15 degrees left uterine displacement. Sensory level of anesthesia was assessed using cold sensitivity to ice at 5 minutes, 10 minutes, and at the end of surgery.

Outcome Measurements

Numerical rating scores (NRS, an 11-point scale where “0” is no pain and “10” is maximum pain) were used to assess pain severity. The nurse caring for the patient, and blinded to the study protocol, recorded the pain score in the electronic medical record.

Postoperative pain scores and opioid consumption were recorded in the post-anesthesia care unit (PACU), 4, 8, 12, 24, and up to 96 hours postoperatively. Analgesic requirements were converted to morphine equivalents based on a validated conversion chart.¹⁴ Patients were given institutional post cesarean analgesia protocol. Patients were given fixed acetaminophen 650mg every 8 hours alternating with naproxen sodium 500 mg every 12 hours for the first 24 with on demand analgesia of opioids medications throughout the hospital stay. If pain relief was inadequate, patient received on demand opioid regimen as follow: NRS ≥ 7, patients received 10 mg oxycodone by mouth. NRS ≥ 3 but less than 7 patients received 5 mg oxycodone by mouth every 4 to 6 hours. In the immediate postoperative period, patients received hydromorphone intravenously as follow 200 to 400 microgram IV every 10 to 15 min total of 1 mg.

Patients in the postpartum, period were monitored according to the American Society of Anesthesiology practice guidelines for patients receiving neuraxial opioids. In brief, SpO₂ was used continuously for 24 hours, respiratory rate every hour for 12 hours and every 2 hours for the next 12 hours. Opioid sedation scale was used based on the following: anxious/agitated=1; cooperative=2; sedated but responsive=3; asleep but responsive=4; asleep sluggish response=5; asleep unresponsive=6. We set our target range as 2 to 3.

Statistical Analysis

The data was first assessed for normality of distribution. Descriptive analyses were then performed and the data were reported as mean and standard deviation when normally distributed, and as median and interquartiles when not normally distributed. Mann-Whitney test or *t*-test were used as appropriate.

The effect of the treatment (ondansetron) on the 2 outcome variables (pain scores and opioid consumption) was assessed using linear mixed effects models (LMMs) to account for correlations between repeated measures. LMMs were used because they are robust for non-normally distributed data. The groups (placebo vs. ondansetron) and the linear and quadratic association with time, in hours, were modeled as fixed effects, and patients were modeled as random effects. The following linear mixed effects model was fitted:

$$y_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \beta_3 x_{3ij} + b_{i0} + \varepsilon_{ij}$$

where y_{ij} is the outcome variable (ie, pain scores, opioid consumption), x_{1ij} , x_{2ij} , and x_{3ij} are the linear time, quadratic time, and Group (Placebo/Ondansetron) fixed effects for observation j in patient i , b_{i0} is the random intercept for patient i , and ε_{ij} is the error for observation j in patient i .

Results

In this study, we assessed the effect of the 5HT₃ antagonist ondansetron on opioid tolerance in pregnant patients undergoing cesarean delivery under spinal anesthesia. We found that intravenous ondansetron administration did not significantly affect postoperative pain scores and opioid consumption when compared with placebo in patients receiving intrathecal opioids prior to cesarean delivery.

A total of 86 patients were included in this study, 42 patients in the placebo group and 44 in the ondansetron group. No differences between the two groups were found in age, body mass index, American Society of Anesthesiologists (ASA) scores, duration of surgery, or sensory and motor block characteristics (Table 1).

Postoperative pain scores and opioid consumption averaged at each time points are presented in Table 2 and Figures 1 and 2. For both pain scores and opioid consumption, the quadratic relations with time were statistically significant (both $P < 0.0001$). Averaged across all patients, results showed that pain scores increased for the first few hours postoperatively and subsequently leveled off over time. On the other hand, the opioid consumption decreased

during the first few hours of post-op, but increased over time. After taking into account the changes in pain scores and opioid consumption over time, there was no statistically significant difference between the placebo and ondansetron group in postoperative pain scores ($P = 0.95$) or opioid consumption ($P = 0.68$).

Discussion

Opioid tolerance is defined as an increase in the dose of opioids required for maintaining adequate analgesia in patients having pain. Opioid tolerance can develop after long term or short-term exposure to opioids. Several reports also suggest tolerance to opioids develops as early as in the perioperative period.^{7,8} This is called acute opioid tolerance (AOT). AOT has been demonstrated in both the general and the obstetrical population following intravenous or intrathecal administration of opioid.^{1,7} The hypothesis that ondansetron may affect acute opioid tolerance derives from earlier animal and human studies of opioids and alcohol dependence. The 5-HT₃ receptor is known to have multiple functions including those related to nausea and vomiting, pain processing, the drug reward system and anxiety.⁹ Animal evidence of the effects of ondansetron on acute opioids tolerance were described by De-Yong Liang et al who found that systemic or intrathecal administration of ondansetron significantly prevented and reversed opioid tolerance in mice. Ondansetron was also found to reverse spontaneous hyperalgesia in a morphine-dependent mice model.¹⁰ Additionally, the role of the serotonergic system in pain modulation is relatively well described. Various animal studies found the 5HT₃ receptor to have pro-nociceptive functions and the administration of systemic or intrathecal ondansetron blocked this effect.⁹

The results of our study differ from those of Liang et al.⁹ The lack of effect found in our study could possibly be explained by the idea that animal models used to assess tolerance may not produce reliable results because pain behaviors include both a (nociceptive component) and emotional detachment (psychomotor component) from pain.¹⁵

The transfer of ondansetron through the blood brain barrier is estimated to be less than 10% of the intravenous dose.¹⁶ Therefore 8 mg of intravenous ondansetron in our study could result in CNS levels that are high enough to exert its action. However, we cannot know the necessary fraction of ondansetron or that crossed the blood brain barrier in order to modulate the 5HT₃ receptor to affect tolerance or to produce analgesic effects. In this context, Peters et al suggested that a suprathreshold stimulus may be necessary to recruit descending serotonergic pathways to observe the effect of ondansetron on spinal neuronal excitability and behavioral hypersensitivity following spinal nerve ligation in a rat model¹⁷. It could be that in our study, the surgical stimulus is blunted secondary to spinal anesthesia and therefore the serotonergic descending pathways may have not been recruited. Another explanation for the lack of effect seen in our study is that the dose of intrathecal opioids may have been too low to induce a significant amount of tolerance. Nonetheless, addition of 25 µg of intrathecal fentanyl to subarachnoid bupivacaine increased opioid requirement between 6 and 23 hours after cesarean delivery by 63 %. ¹¹ Intrathecal fentanyl (5, 10, or 25 µg) added to subarachnoid bupivacaine and morphine did not affect opioid use but increased postoperative score.¹ Both studies indicate that modest doses of intrathecal fentanyl can induce opioid tolerance

Several variables were accounted for in this study, including the type of procedure and anesthetic, components of the spinal anesthetic, dose of ondansetron, and timing of ondansetron administration. Despite several variables being controlled, there are still limitations of this study and potential confounding variables. Instead of utilizing patient-controlled analgesia with only one type of opioid, participants in this study received several types of opioids postoperatively; opioid consumption was determined after conversion to morphine equivalents via an equianalgesic table.¹⁸ All participants in this study also received NSAIDs and acetaminophen for postoperative pain; thus, non-opioid pain medications given postoperatively could have altered opioid consumption. However, the use of a multimodal approach to postoperative pain control likely makes the results of this study more universally applicable, as this approach is commonly used in clinical practice. It is now common for patients receiving neuraxial opioid to also receive intraoperative dexamethasone for prophylaxis of nausea and vomiting. This is very important because dexamethasone has been found to enhance analgesia compared with placebo when given prophylactically for neuraxial opioid-induced nausea and vomiting. Dexamethasone positive effects on pain would have confounded our results.¹⁹ However this is unlikely, as our patients did not receive dexamethasone intraoperatively.

While our patient population at the time of cesarean delivery was not on opioid therapy, patient did not receive opioid in the prenatal period either based on their electronic medical record and patient's medication list. Albeit, one patient was on chronic opioids, but was excluded from the study analysis. The presence of opioids use during pregnancy in our study group would have affected our results, as these patients may already be tolerant to opioids. In this present study, we only assessed the effect of ondansetron on AOT, which can be operationally defined as an increase in the dose of opioids required for maintaining analgesia. The assessment of neuropathic pain using the DN4 questionnaire would have added strength to our study, as it will provide a clear delineation between AOT and opioid induced hyperalgesia; however, this was not feasible given the study context. We acknowledge the lack of an a-priori power analysis in the current study; as described in the methodology section, the current study is a secondary data analysis using data collected from a study with a different study objective. As we did not foresee the use of the data for the current study at the time of data collection, an a-priori power analysis was not conducted. The nonsignificant findings of the current study may be due to low power or a “real” small effect size; in this instance, one may suggest the lack of significance must be due to a small effect size if the post-hoc power is high. However, we believe that post-hoc power calculations are inappropriate because the calculated power (ie, “observed” power obtained from the model estimates) is a function of the *P*-values of the model estimates, meaning that post-hoc power analysis does not provide additional information to the results²⁰. However, power analysis for future studies can be performed with the current data.

In summary, within the realm of this secondary analysis, we could not substantiate a measurable effect of ondansetron on opioid consumption when administered during caesarean section with subarachnoid anesthesia, and further studies may be necessary.

Acknowledgments

Funding: This study is partially supported by the research training grant 5-T32-MH 13043 from the National Institute of Mental Health [Dr Siny Tsang, PhD]

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Figure 1.

Graph depicting pain scores after surgery from PACU until discharge from hospital.

Only one patient remained in the hospital at 120 hours.

Y-axis: Numerical Rating scale

X-axis: Time in hours

(PACU: post-anesthesia care unit)

Figure 2.

Graph depicting opioid consumption after surgery from PACU until discharge from hospital.

Only one patient remained in the hospital at 120 hours.

Y-Axis: Mean opioid consumption in milligrams of morphine equivalent.

X-Axis: Time in hours.

Table 1

Demographic and Intraoperative characteristics.

Characteristic	Group A (Ondansetron) n = 44		Group B (Placebo) n = 42		P-value
	Mean	SD	Mean	SD	
Age	30	± 5.43	28	± 5.41	0.18
BMI	32	± 5.58	34	± 7.90	0.21
ASA I	8	18%	5	12%	NA
ASA II	36	82%	37	88%	
Time to Delivery in (minutes)	19	± 8.91	20	± 7.40	0.24
Intraoperative fluids (mL)	2190.24	± 663.35	2297.37	± 667.18	0.43
Estimated blood loss (mL) ^{**}	750	[600, 850]	700	[500, 1000]	0.89 [§]
Drug to spinal (minutes) [*]	8.20	± 4.80	9.12	± 4.95	0.31
Spinal to incision (minutes)	16.12	± 3.46	16.76	± 3.01	0.38
Spinal to delivery (minutes)	35.46	± 10.58	37.49	± 8.41	0.34

BMI = body mass index, ASA = American society of anesthesiologists score

^{**} Presented as median and [first quartile, third quartile].[§] Using Mann-Whitney test, as they are not normally distributed data.^{*} The drug was administered 5-minute before spinal anesthesia attempt, even with the variation in time taken between anesthesiologists to perform the successful attempt, the time still not significant between the 2 groups.

Table 2

Results of linear mixed effects model examining the effect of ondansetron versus placebo on pain scores and opioid consumption over time.

Variable	Estimate	S.E.	<i>t</i>	<i>P</i>
Pain scores				
Intercept	2.22	0.23	9.55	< 0.0001
Time	2.23	0.27	8.27	< 0.0001
Time ²	-0.49	0.08	-6.13	< 0.0001
Group	0.02	0.29	0.06	0.95
$\sigma^2_{\text{patients}}$	0.94			
Opioid consumption				
Intercept	-0.43	0.84	-0.51	0.61
Time	15.41	0.93	16.56	< 0.0001
Time ²	-3.22	0.24	-13.27	< 0.0001
Group	0.35	0.85	0.41	0.68
$\sigma^2_{\text{patients}}$	6.97			

Group (Placebo/Ondansetron), Time, and Time² were modeled as fixed effects; patients were modeled as random effects. Time = linear relation between variables and time (in days). Time² = quadratic relation between variables and time (in days). $\sigma^2_{\text{patients}}$ = estimated variance between patients.