Ondansetron Given Intravenously to Attenuate Hypotension and Bradycardia During Spinal Anesthesia in Cesarean Delivery: A Literature Review

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Abstract

Spinal Anesthesia is the most common type of anesthesia provided to the parturient for cesarean section. An undesired side effect often seen with the administration of a spinal anesthetic is hypotension and bradycardia. The Bezold-Jarisch reflex is the likely cause of hypotension and bradycardia associated with spinal anesthesia. This reflex is elicited by stimulation of peripheral serotonin receptors 5-hydroxytryptamine (5-HT3 type). Ondansetron is a selective serotonin 5-HT3 receptor antagonist. Current research in animals, obstetric and non-obstetric populations indicates that 5-HT3 antagonism may abolish the Bezold-Jarisch reflex. However, further research is needed to determine the effectiveness of using ondansetron in preventing hypotension and bradycardia post spinal anesthesia in the obstetric population.

Keywords: Ondansetron, Bezold-Jarisch reflex, obstetric, 5-HT3
Ondansetron Given Intravenously to Attenuate Hypotension and Bradycardia During Spinal Anesthesia in Cesarean Delivery

Spinal Anesthesia is the most common type of anesthesia provided to the parturient for cesarean section. An undesired side effect often seen with the administration of a spinal anesthetic is hypotension and bradycardia. Current treatments include fluids and vasopressors, with the latter known to have maternal and fetal side effects. The Bezold-Jarisch reflex is the likely cause of hypotension and bradycardia associated with spinal anesthesia. This reflex is elicited by stimulation of peripheral serotonin receptors 5-hydroxytryptamine (5-HT₃ type). Ondansetron is a selective serotonin 5-HT₃ receptor antagonist. Current research indicates that 5-HT₃ antagonism may abolish the Bezold-Jarisch reflex response to spinal anesthesia.

Existing research concerning the undesired cardiovascular effects of spinal anesthesia has been conducted on the non-obstetric, obstetric, and neonatal patient. A knowledge gap exists, stimulating the current literature review on the use of ondansetron to prevent undesired cardiovascular effects of spinal anesthesia. Because spinal anesthesia is one of the most common types of anesthesia provided to the parturient during a cesarean section, the use of a 5-HT₃ antagonist may be beneficial to prevent bradycardia and hypotension. The purpose of this literature review is to demonstrate that further research needs to be conducted in the obstetric population with the administration of ondansetron to address hypotension and bradycardia caused by the Bezold-Jarisch reflex during spinal anesthesia.

Compared to general anesthesia, regional anesthesia offers reduced maternal mortality, the ability to use fewer drugs, direct maternal and paternal experience of childbirth, and the capability to decrease blood loss while providing excellent postoperative pain control. Despite
all of its advantages, spinal anesthesia is not free from adverse effects, including potentially harmful hypotension and bradycardia. The incidence of hypotension and bradycardia in the parturient patient is 52.6% and 2.5% respectively. This hypotension and bradycardia causes a decrease in systemic vascular resistance and myocardial contractility. In addition, peripheral vasodilatation with a redistribution of central blood volume to the splanchnic circulation and lower extremities occurs. Bradycardia may be due to unopposed parasympathetic activity, increased baroreceptor activity, or the Bezold-Jarisch reflex.

The Bezold-Jarisch Reflex is an inhibitory response usually described as a cardioinhibitory reflex. The heart is innervated by the vagus nerve, which consists of two major fiber types, 25% are myelinated fibers which originate in the walls of the atria and 75% are nonmyelinated fibers found in the walls of all four cardiac chambers. Animal studies have shown that the Bezold-Jarisch reflex originates in cardiac receptors with nonmyelinated type C vagal fibers creating the afferent limb of the reflex. These receptors are both mechanosensitive and chemosensitive and when stimulated produce bradycardia, peripheral vasodilation and hypotension. These chemoreceptors are sensitive to several different chemicals including serotonin.

Serotonin, 5-hydroxytryptamine (5-HT), is one class of monoamine neurotransmitters produced by enterochromaffin cells in the human body. The majority of serotonin is in the gastrointestinal system while the remaining serotonin is located within the central nervous system. Serotonin is important for many physiological roles within the human body such as, development, cardiovascular, gastrointestinal, endocrine function, sensory perception and behavior. Currently there are 14 different 5-HT receptors identified, and with the exception of 5-HT3, which is a ligand-gated channel, all other receptors are a G-protein coupled receptor.
5-HT₃ receptors are located in both the peripheral and central nervous system in humans, and are found both pre- and postsynaptically. It is thought that the stimulation of these peripheral 5-HT₃ receptors results in increased parasympathetic activity and decreased sympathetic activity, resulting in bradycardia, vasodilation, and hypotension.

Ondansetron is a selective serotonin 5-HT₃ receptor antagonist, and is currently approved by the Food and Drug Administration (FDA) for treatment of nausea and vomiting caused by chemotherapy, radiation therapy, and surgery. Side effects associated with the use of ondansetron include: diarrhea, headache, constipation, weakness tiredness, and dizziness. The FDA has assigned ondansetron to pregnancy category B, which means quality studies in human parturients receiving this medication have not yet been conducted. However, animal studies demonstrated no harm to their offspring. A limited study was conducted in 176 pregnant females which showed that ondansetron does not appear to be associated with an increased risk for major malformations above baseline. Although limited human data exists, ondansetron is frequently given to parturient patients to help prevent nausea and vomiting without any reported maternal or fetal harm.

Many research studies have been conducted to show the correlation between 5-HT₃ receptors and the cardiovascular effects via the Bezold-Jarisch reflex. A study done at the University of Connecticut investigated whether granistron, a 5-HT₃ antagonist, could alter hypotension and bradycardia caused by the Bezold-Jarisch reflex utilizing the hemorrhagic model. In this quantitative experimental study, rabbits were randomized to receive 5 micrograms (mcg) of granistron or 5 milliliters (ml) of normal saline. Rabbits were observed and after 5 minutes of administration of granistron (n=5) or saline (n=6), hemorrhage was induced until blood pressure reached a target low of 80 millimeters of mercury systolic blood
pressure. Acute blood loss in hemorrhagic animals causes a biphasic response. The first phase is characterized by an increase in heart rate and systemic vascular resistance. The second phase is characterized by bradycardia and hypotension which has been termed the Bezold-Jarisch reflex. This reflex is paralleled in humans. This study showed that the administration of granistron significantly attenuated the decline of heart rate in rabbits, suggesting that granistron does not affect the first phase of the hemorrhagic model, but does attenuate the lowering of heart rate seen in phase two. The study also concluded that the granisetron group was more resistant to lowering of blood pressure which was shown by significantly larger amounts of blood being removed in the granistron group when compared to the normal saline group.

In a case study reported by Marnitek patient developed asystole after the administration of a spinal anesthetic. A 50 year old healthy male presented for tibial osteotomy under spinal anesthesia. Following intravenous volume administration with 500 ml of lactated ringers and sedation with intravenous remifentanil 25 mcg, a spinal anesthetic was administered. Vital sign measurements were normal at the time of spinal administration. Thirteen minutes after spinal administration, the surgeon injected the incision site with local anesthetic containing epinephrine. One minute later the patient’s electrocardiogram (ECG) showed a sinus bradycardia; blood pressure and oxygen saturation remained stable. Several minutes later the patient went into cardiovascular collapse. Atropine 0.6 milligrams (mg) was given intravenously followed immediately by ondansetron 4 mg intravenously. Before chest compressions were initiated, vital signs returned with no further complications. The asystole in this patient may be explained by exogenous epinephrine that triggered the Bezold-Jarisch reflex, and the administration of ondansetron may have antagonized the afferent vagal 5-HT3 receptors sufficiently to block the reflex. The authors of this study stated that further research was needed
to examine the effects of ondansetron on the Bezold-Jarisch reflex.

According to Saxena and Villalon, intravenous bolus injections of 5-HT, phenylbiguanide, and 2-methyl-5-HT in anesthetized rats, rabbits, cats, ferrets, dogs, and guinea pig elicit short lasting bradycardia that can be blocked by a 5-HT_{3} receptor antagonist. The results of the study demonstrated that the bradycardia due to 5-HT injection results from an effect on cardiac receptors, specifically 5-HT_{3}, causing a Bezold-Jarisch reflex.

A study conducted by Owczuk et al., verified the hypothesis that blockade of type 3 serotonin receptors by intravenous ondansetron administration may reduce hypotension and bradycardia induced by spinal anesthesia in non-obstetric patients. Seventy-one patients were selected and randomized for the study. Thirty-six patients received intravascular ondansetron 8 mg and thirty-five patients received a placebo of normal saline five minutes prior to the administration of spinal anesthesia. Hemodynamic measurements were recorded at designated intervals prior to and after administration of spinal anesthesia. The authors of this study reported higher minimal systolic and mean blood pressure values in patients who were given 8 mg intravenous ondansetron before spinal anesthesia, compared to patients in the placebo group.

A study in Kolkata, India conducted by the Institute of Post Graduate Education and Research Department of Anesthesia evaluated the effect of ondansetron on the hemodynamic response following subarachnoid block in parturients undergoing elective cesarean section. The authors hypothesized that the use of IV ondansetron in non-laboring obstetric patients would reduce spinal-induced hypotension and bradycardia by blocking 5-HT_{3} receptors and preventing the Bezold Jarisch reflex. Fifty-two parturient patients scheduled for elective cesarean section were randomly selected into two groups. The parturient patients were American Society Anesthesiology physical status I, between 20 and 40 years of age, and undergoing an elective,
lower segment caesarean section. Before subarachanoid block twenty-six patients in Group O received ondansetron 4 mg diluted to 10 ml and twenty-six patients in Group S received normal saline 10 ml. The spinal technique was performed in the sitting position at L3-4 or L4-5 and 0.5% hyperbaric bupivacaine 2 mL was administered after confirmation of cerebrospinal fluid through a 25- or 26-gauge Quincke spinal needle. Heart rate, systolic/diastolic, mean arterial pressure, oxygen saturation were recorded at the time of spinal administration and at 2-min intervals up to 20 minutes, followed by 5 minute intervals until end of surgery. Results showed decreases in mean arterial pressure were significantly less in Group O than Group S from 14 min until 35 min. Patients in Group O required significantly less vasopressor (P = 0.009) and had significantly fewer incidences of nausea and vomiting (P = 0.049).

Given that spinal anesthesia is the most common type of anesthetic given for cesarean section, it is not uncommon for parturients to experience hypotension and less commonly bradycardia. Current management of hypotension post-spinal anesthesia in cesarean section is fluid management and the use of vasopressors. The use of a crystalloid or colloid fluid bolus prior to spinal anesthetic administration for cesarean section has been used successfully to combat hypotension. In a study conducted by Ngan, Khaw, Lee, Ng & Wong, an experimental group received 15 ml/kg colloid bolus just prior to spinal anesthesia for cesarean section. When compared to the control group, the experimental group had higher systolic blood pressures within the first ten minutes following spinal anesthesia. Nonetheless, participants from both study groups still required a vasopressor infusion to maintain systolic blood pressures within 90-100% of baseline.

Many studies have been done with the utilization of phenylephrine and ephedrine in the obstetric population. Both vasoactive drugs successfully treat post-spinal hypotension but have
undesired side effects. Ephedrine is a synthetic, non-selective, non-catecholamine, sympathomimetic vasopressor.\textsuperscript{1} The side effects that coincide with the use of ephedrine include supraventricular tachycardia, tachyphylaxis, and fetal acidosis.\textsuperscript{16} Ephedrine causes B-adrenergic stimulation as it crosses the placenta and increases fetal catecholamine levels. Phenylephrine is a pure alpha-agonist and is associated with maternal bradycardia.\textsuperscript{16} Although the use of vasoactive drugs in the parturient population has been shown to be effective, their use does not come without potential harmful fetal effects. Finding an alternative to these medications, such as ondansetron may decrease the risks of spinal anesthesia in the cesarean section patient.

In conclusion, if ondansetron can successfully block the Bezold-Jarisch reflex it may be used successfully to treat post-spinal hypotension without the side effects of vasoactive drugs. Anesthesia providers may improve patient outcomes by minimizing the use of vasopressors post spinal anesthesia with the simple intervention of prophylactic ondansetron. This literature review highlights the use of a $5\text{HT}_3$ antagonist as a successful prevention of hypotension and bradycardia caused by the Bezold-Jarisch reflex in animals, obstetric and non-obstetric patients. Further research is needed to determine the effectiveness of using ondansetron in preventing hypotension and bradycardia post spinal anesthesia in the obstetric populations. With a decreased incidence of bradycardia and hypotension, anesthesia providers can provide improved outcomes for their parturient patients and neonates. As a result, patient satisfaction will be improved and anesthesia providers can practice with an increased margin of safety.
References


