5-1-2018

Effect of Intravenous Ondansetron on Blood Pressure when Administered Prior to the Establishment of Subarachnoid Anesthesia

Brandon Boyd

Effect of Intravenous Ondansetron on Blood Pressure when Administered Prior to the Establishment of Subarachnoid Anesthesia

By

Brandon Boyd

Bachelor of Science in Nursing, University of North Dakota, 2012

An Independent Study

Submitted to the Graduate Faculty

Of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

University of North Dakota

December 2018

PERMISSION

Title Effect of Intravenous Ondansetron on Blood Pressure when Administered Prior to the Establishment of Subarachnoid Anesthesia

Department Nursing

Degree Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing and Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in his absence, by the chairperson of the department or the dean of the School of Graduate Studies. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Abstract

Title: Effect of Intravenous Ondansetron on Blood Pressure when Administered Prior to the Establishment of Subarachnoid Anesthesia.

Background: Hypotension is a known effect of spinal anesthesia. In recent years, ondansetron has been explored as another means of attenuating spinal-anesthesia induced hypotension (SIH).

Purpose: This case study looks at one clinical application of this intervention and examines the literature on the topic to determine the usefulness of administering IV ondansetron prior to spinal anesthesia.

Process: In the clinical setting, IV ondansetron was given prior to administering spinal anesthesia; this case is discussed in detail. The databases CINAHL and PubMed were searched to attain 13 randomized controlled trials which studied this intervention. These studies were reviewed and recommendations were made based on the literature.

Results: More uniform research should be done on this topic. However, it can be recommended to administer 4 mg ondansetron intravenously about 5 minutes before establishing spinal anesthesia. Existing methods of preventing and treating SIH should still be employed when necessary.

Implications: IV ondansetron can be used as an additional tool to help prevent spinal-induced hypotension, potentially minimizing adverse outcomes associated with hypotension resulting from spinal anesthesia.

Keywords: Ondansetron, hypotension, spinal anesthesia, spinal-induced hypotension

Background

Spinal anesthesia is the administration of local anesthetic agents, and other adjunct medications into the subarachnoid space with the purpose of blocking sensory and motor transmission at the roots of spinal nerves. It was first successfully used in 1898 on a patient having surgical resection of a tuberculous ankle joint who had previous adverse reactions to general anesthesia. Fifteen milligrams (mg) of cocaine was administered intrathecally. The patient was pain free during surgery and had minimal adverse effects post-operatively including nausea and headache (Wulf, 1998). Today, spinal anesthesia is commonly used for various procedures involving the lower extremities, perineum, and abdomen (Nagelhout, 2014).

Hypotension is a known side-effect of spinal anesthesia. Tubog, Kane, and Pugh (2017), cite the incidence of spinal anesthesia-induced hypotension (SIH) at 15-33%. Some sources indicate an even higher (as high as 80%) prevalence (Wang et al., 2014). The variable prevalence rate can be owed to individual patient factors, including comorbidities and anesthetic technique. Many sources indicate that the incidence of hypotension is greater in the obstetric population than in other patient populations. Hypotension has negative implications on every population as it can result in decreased perfusion and oxygen delivery to vital organs. Further implications exist in the obstetric population, “hypotension during spinal anesthesia for cesarean delivery remains a common clinical problem that is associated with morbidity for both mother (nausea and vomiting) and fetus (fetal acidosis)” (Ngan Kee, Khaw, & Ng, 2005, p. 744).

Often, the current preventative treatments are not sufficient, requiring pharmacological intervention which becomes a reactive strategy rather than proactive. Recently, a new measure, the administration of intravenous ondansetron prior to administering the spinal anesthetic, has come into question as a viable preventive strategy to mitigate SIH. If this proves to be true, it

could improve the safety of spinal anesthesia by decreasing the incidence of hypotension and its negative effects.

Case Report

A 64-year-old, 5'2", 72.5 kg female, presented for a total knee arthroplasty. She had osteoarthritis of both knees requiring replacement, however, only the left knee was to be replaced. Her past medical history included asthma, GERD, and hypertension. She had a past surgical history of rotator cuff repair, tubal ligation, and knee arthroscopy. Her home medications included albuterol, Celebrex 200 mg, gabapentin 100 mg, hydrochlorothiazide 25 mg, and omeprazole 20 mg. She had no known drug allergies and was classified as an ASA 2. Pre-anesthetic evaluation did not reveal any abnormal labs or studies. Physically, she presented with knee pain. Her airway evaluation was unremarkable. Baseline vital signs were as follows: BP 138/84, HR 74, RR 16, SpO2 95%, and temperature 98.9 degrees Fahrenheit. In the preoperative holding room, an 18-gauge IV was started in her left hand and she was given 2 mg midazolam.

The patient was brought to the OR at 0631, was given 4 mg ondansetron intravenously, and was given a bolus of 500 mL lactated ringers, while being attached to standard monitoring. Initial BP while supine was 135/85 (101) with a HR of 79. Additionally, 6 mg of midazolam (now a total of 8 mg) was administered prior to the block per the anesthesiologist's request. She was positioned in a sitting position on the OR table and a spinal block was administered at 0645. The following medications were administered intrathecally: 1.6 ml of bupivacaine 0.75% (12 mg) and 25 mcg of fentanyl. After the block, she was immediately placed in a supine position and a propofol infusion was started at a rate of 12.5 mcg/kg/min. Oxygen was also applied via nasal cannula at three liters per minute. Additionally, one gram of Ancef and one gram of

tranexamic acid were administered during this time. The first BP after the block was established was 109/68 (88). Ten minutes after the block was established the BP dropped to 101/60 (73) and 100 mcg of phenylephrine was administered. This was the only dose of vasopressor given. The tourniquet was inflated at 0708 and incision was made 0710. Systolic blood pressures after the block ranged from 98 to 120, and diastolic blood pressures ranged from 53-68. The lowest MAP that was encountered was 68 and occurred 85 minutes after the block was administered. Heart rate throughout the case ranged from 58-80 BPM. The tourniquet was let down at 0801 and a second gram of tranexamic acid was given. The propofol infusion was discontinued at 0813. A total of 1,200 mL LR was given throughout the case and 225 mL was determined to be the estimated blood loss. The patient was transferred to the PACU at 0831 with the following vital signs: BP 108/64, HR 61, SpO2 100%, RR 14. It was realized that the surgeon forgot to apply the subcutaneous layer of sutures and he decided to do this at the bedside in the PACU. To facilitate this, two additional mg of midazolam were administered.

Discussion

Spinal Anesthesia

Spinal anesthesia is the injection of medications into the subarachnoid space, which contains cerebrospinal fluid, with the purpose of blunting or abolishing sensory and/or motor nerve transmission (Nagelhout & Plaus, 2014). It's advantages over general anesthesia include less nausea and vomiting, less urinary retention, reduced opioid requirement, greater mental awareness, less intraoperative blood loss, decreased incidence of thrombotic events, and less risk of developing a post-op ileus. Additionally, patients have improved respiratory and cardiac stability, and are quicker to drink, eat, and ambulate post-operatively (Nagelhout & Plaus, 2014).

Indicated procedures for the use of spinal anesthesia include those involving the lower extremities, perineum, and abdomen. It is especially useful for ambulatory procedures as many complications of general anesthesia are avoided, greatly decreasing the possibility for unforeseen overnight hospital stays. Spinal anesthesia is very useful in obstetric procedures as it provides adequate pain control while still allowing baby and mother interaction post-delivery. Additionally, patients undergoing urologic procedures, such as TURP, can benefit from a spinal anesthetic as they can alert the urologist of feelings of bladder overdistention, thus reducing the risk of rupture. Maintaining alertness in these patients also has benefit in that it allows the anesthetist to detect changes in mental status which is often the first sign of TURP syndrome (Nagelhout, 2014).

There are some contraindications to spinal anesthesia. Absolute contraindications include patient refusal, infection at the injection site, symptomatic hypovolemia, coagulopathy, indeterminate neurological disease, and increased intracranial pressure (NYSORA, 2017). Patients with a fixed volume cardiac state (such as hypertrophic cardiomyopathy or severe atrial stenosis) or with severe aortic stenosis (valve area < 1.0 cm^2) will not tolerate bradycardia and hypotension as it will lead to coronary hypoperfusion (Nagelhout, 2014). Relative contraindications are infection elsewhere, not at the injection site, unknown duration of surgery, sepsis, uncooperative patient, preexisting neurological deficits, demyelinating lesions, and spinal deformity (Butterworth, Mackey, & Wasnick, 2013).

There are side effects to spinal anesthesia as well. The severity of these are often dependent on the level of the block. Cardiovascular side effects can include hypotension, and bradycardia. Vasomotor tone is influenced by autonomic efferent fibers arising from T5 – L1 spinal levels. Cardiac accelerator nerve fibers exist at spinal levels T1-T4. Pulmonary side

effects are rare, but the phrenic nerve can be impacted if the block rises to cervical nerves 3 – 5, causing decreased diaphragm function (Butterworth, Mackey, & Wasnick 2013). Nausea and vomiting can occur in up to 20% of patients who receive neuraxial anesthesia. This is primarily a result of hypotension and decreased perfusion to the medulla of the brain, but can also be a result of increased GI peristalsis due to dominance of parasympathetic input. Finally, with spinal anesthesia, there is risk of dural puncture and CSF leak, resulting in what is referred to as a postdural puncture headache. This occurs as the brain loses its "cushion" which is provided by circulating CSF. The risk of this side effect can be minimized by using smaller gauge, pencil point needles (Nagelhout & Plaus, 2014).

Mechanism of Spinal Anesthesia-Induced Hypotension

When local anesthetic agents are introduced into the subarachnoid space, the drug spreads from the injection site and its concentration gradient decreases as it moves further from this area. A differential blockade results as only the most "local anesthetic susceptible" neurons will be blocked in the areas of this decreased concentration gradient. Type B autonomic nerve fibers (sympathetic fibers) are of the most susceptible neurons as they are relatively small in diameter and lightly myelinated. Because of this, sympathetic neurons tend to be blocked up to six spinal segments above somatic sensory fibers, which are generally larger in diameter and more heavily myelinated (Nagelhout & Plaus, 2014).

Nagelhout & Plaus (2014) describe the cardiovascular effects of spinal anesthesia, "Blockade of the sympathetic nervous system causes arterial vasodilation, decreased systemic vascular resistance, venous pooling, and reduction in venous return. These changes cause a redistribution of blood that often results in hypotension" (p. 1083). If the block reaches the cardiac accelerator fibers, at levels T1 to T4, this hypotension can be amplified by the

development of bradycardia and decreased cardiac output. In addition to the decreased sympathetic outflow, the cardiovascular response to spinal anesthesia is affected by baroreceptor reflexes, volume receptor reflexes, and the Bezold-Jarisch reflex (Nagelhout & Plaus, 2014).

The Bezold-Jarisch reflex (BJR) "is a cardioinhibitory reflex producing bradycardia, hypotension, and cardiovascular collapse via nonmyelinated, type C fibers whose terminals lie in the chambers of the heart" (Tubog, Kane, & Pugh, 2017). Trebelsi et al. (2017) indicate that 5-hydroxytriptymine subtype 3 (5-HT3) receptors located peripherally may aid in inducing the BJR. Terkawi et al., 2015 further explain this, "This reflex is mediated by serotonin receptors (5-HT3 subtype) located on the vagus nerve and within the wall of cardiac ventricles. They are activated by serotonin release in response to systemic hypotension and cause an increase in efferent vagal signaling" (p.344).

Detrimental Effects of Spinal-Induced Hypotension

Perfusion to vital organs depends on adequate blood pressure. Hypotension decreases perfusion and oxygen delivery which, if severe, will cause ischemia and tissue death. Ortiz-Gomez et al. (2014) outlines the detriments of hypotension in the parturient, including "maternal nausea and vomiting, and in severe cases unconsciousness, pulmonary aspiration, and placental hypoperfusion with fetal hypoxia, acidosis, and neurologic injury" (p. 138). Wang et al. (2014) adds neonatal apnea to this list of hypotension related complications.

In non-obstetric populations, patients may more frequently have comorbidities, such as hypertension or vascular disease, which might place them at risk for cerebral or myocardial ischemia related to dramatic decreases in blood pressure. Hines and Marschall (2012) state, "Chronic hypertension is a cardiovascular, cerebrovascular, and renal risk factor" (p.111-112). They elaborate by citing intraoperative hypotension as a complicating factor in these patients

(Hines & Marschall, 2012, p.112). Furthermore, interventions to correct hypotension, such as volume replacement or administration of ephedrine, might be risky in elderly patients with heart failure or history of myocardial ischemia (Owczuk et al., 2017). Volume overload can exacerbate heart failure, and ephedrine can increase myocardia oxygen demand via tachycardia. Compromised coronary circulation may not have the ability to increase oxygen supply to meet this demand, which could result in the development of ischemia (Hines & Marschall, 2013, p.1).

Traditional Treatments for SIH

Common preventative and treatment measures for SIH have included positioning, lower leg compression, loading and co-loading of crystalloids, and administration of alpha and beta-adrenergic agonists (Tubog, Kane, & Pugh, 2017). Positioning in trendelenburg can help to increase venous return, as will lower leg compression, however a large reservoir for volume is in the splanchnic and GI circulation which leg compression is unable to aid in correcting. Pre-loading of crystalloids has not proven effective as much of the volume third spaces prior to the administration of the block. In addition, patients with cardiac or renal deficits, may not tolerate the volumes used for pre-loading (10-20 ml/kg). Vasopressors are reactive treatments to hypotension that develops from subarachnoid anesthesia, and while effective, may possess some negative effects. Pure alpha-adrenergic agonists, such as phenylephrine, might exacerbate bradycardia that may be brought on by the SAB, and though mixed alpha- and beta-adrenergic agonists (ephedrine) can be effective, some patients may not tolerate the increase in HR that accompanies their administration (Butterworth, Mackey, & Wasnick, 2013). Other limitations to ephedrine can include a relatively slow onset of action and the development of tachyphylaxis (Lee, George, & Habib, 2016). There is clearly no definitive treatment for SIH, which makes new options to prevent this side effect appealing to explore.

Serotonin

Serotonin (5-hydroxytriptymine [5-HT]) is a neurotransmitter which exerts its effects in many ways throughout the body by binding to a variety of receptors. Principally, in the cardiovascular system, serotonin induces vasoconstriction (Brunton, Hilal-Dandan, & Knollmann, 2018). Terkawi et al., (2015) describe this as a result of it binding to 5-HT2 receptors. In the heart, serotonin is both a positive inotrope and positive chronotrope as it binds to various different 5-HT receptors (Brunton, Hilal-Dandan, & Knollman, 2018). However, when it binds to 5-HT3 receptors it will activate the BJR causing bradycardia and hypotension (Terkawi et al, 2015).

The gastrointestinal tract is the primary site of synthesis and storage of serotonin. Different subtypes of serotonin receptors are responsible for both activation and suppression of intestinal smooth muscle action, enhancing or suppressing GI motility. Serotonin which acts on 5-HT3 receptors in the GI tract and in the central nervous system induces the emetic response, causing nausea and vomiting (Brunton, Hilal-Dandan, & Knollman, 2018).

The brain contains all serotonin receptor subtypes. Serotonin is active in the brain in many ways and influences sleep, cognition, sensory perception, motor activity, temperature regulation, nociception, mood, appetite, sexual behavior, and hormone secretion. Other various effects of serotonin include that in the inflammatory response as it is pro-inflammatory via 5-HT2 receptors and may play a role in airway inflammation in diseases such as asthma. Additionally, serotonin is released from platelets to cause a local vasoconstrictor response, promoting hemostasis after vessel damage (Brunton, Hilal-Dandan, & Knollman, 2018).

Ondansetron

Ondansetron is a serotonin receptor subtype 3 (5-HT3) antagonist. It is commonly used as an antiemetic, working to block 5-HT3 receptors in the GI system and in the chemoreceptor trigger zone of the brain. It has a rapid onset and its duration of action is about 6-12 hours (Vargo Anesthesia, 2012). Aside from its central action in the brain, ondansetron will bind to 5-HT3 receptors peripherally, including those within the cardiac ventricles and on the vagus nerve, which help to mediate the BJR (Trebelsi et al., 2017). Binding these receptors prevents induction of the BJR and decreases parasympathetic dominance, lessening the degree of bradycardia and hypotension brought about by spinal anesthesia.

Adverse Effects

The most common adverse effects of ondansetron (and other 5-HT3 antagonists) include diarrhea, fever, and headache (Butterworth, Mackey, & Wasnick, 2013). Wang et al. (2014), also cite constipation and asthenia as potential side effects. There have also been reports of prolongation of the QT interval with these agents (more frequently with Dolasetron), however, this effect has not been linked clinically to any adverse arrhythmias. It may also be important to note that ondansetron is metabolized by the CYP-450 enzymes of the liver, necessitating consideration in its dosing for patients in liver failure (Butterworth, Mackey, & Wasnick, 2013). Finally, in previous years, there has been concern that prenatal exposure to ondansetron can cause adverse outcomes of pregnancy including spontaneous abortion, still birth, major birth defects, preterm delivery, and low birth weight infants. Wang et al. (2014), explain that appropriate exposure to ondansetron does not cause these adverse effects. “Ondansetron administration during the first trimester of pregnancy is not associated with an increased risk for major malformations above baseline” (Wang et al, 2014, p.5214).

Ondansetron Administered Prior to SAB

A total of 13 randomized controlled trials, which explored the effects of intravenous ondansetron administered prior to the establishment of spinal anesthesia, were reviewed. Methods of each trial are similar although there is some variability.

Obstetric Populations

Trabelsi et al. (2015) examined the effect ondansetron has on maternal hypotension and on certain neonatal parameters, including APGAR score, umbilical artery pH, and neonatal lactate levels. They included 80 patients undergoing cesarean section split into two groups, a control group and an intervention group which received 4 mg ondansetron five minutes prior to SAB. Saline (10 ml/kg) was given as a bolus as well. The spinals included 2 ml bupivacaine 0.5% (10 mg) and 10 mcg sufentanil. Hypotension was defined as a drop in BP > 20% from baseline, or MAP < 80 mmHg. They determined that a statistically significant difference existed in the incidence of hypotension (77.5% in the control group, 37.5% in the group which received ondansetron) between groups. They also note that more ephedrine was required in the control group. Of the neonatal parameters, they found higher APGAR scores, lower lactate levels, and higher cord arterial pH in the intervention group (p. 1-7).

Wang et al. (2014) looked at different doses of ondansetron compared to a control group and how it affected hemodynamics in parturient patients undergoing cesarean section. They also looked at neonatal outcomes. One hundred and fifty primiparous patients were split into five equal groups; a control group, and four intervention groups each of which received either 2, 4, 6, or 8 mg of ondansetron 5 minutes prior to establishment of the SAB. All patients were injected with 10 mg bupivacaine intrathecally. After the spinal was performed, LR solution was given rapidly up to 10 ml/kg. After delivery, 10 units oxytocin in 250 ml saline was given at an

unspecified rate. Hypotension was defined as a drop in baseline SBP by 20% or greater. The incidence of hypotension was found to be less in the groups who received ondansetron in 4 mg and 6 mg doses, and these differences were found to be statistically significant. Regarding neonatal outcomes, no significant differences were noted in APGAR scores, birth weight, nor umbilical cord arterial pH between groups. The pH of umbilical cord venous blood, however, was significantly higher in the group which received four mg ondansetron (p. 5210-5216).

Terkawi et al. (2015) had differing results in their study which evaluated ondansetron's effect on hemodynamics in patients undergoing cesarean section. Eighty-six patients were split into two groups, a control group and an intervention group which received 8 mg ondansetron five minutes prior to SAB. All patients were preloaded with 500 ml Hetastarch, and plasmalyte was used as maintenance fluid. The spinal was established using 2 mL of 0.75% bupivacaine (15 mg), with 20 mcg fentanyl, and 100 mcg morphine. Hypotension was defined as SBP < 90 mmHg. They determined there was no significant difference in the development of hypotension between the two groups. They also did not find a difference in amount of vasopressor used to correct hypotension (p. 344-348).

Khouly & Meligy (2016) looked at 102 parturients undergoing cesarean section. A control group which received saline was compared to the intervention group which received 4 mg ondansetron five minutes prior to SAB. Two mL of 0.5% bupivacaine (10 mg) was administered intrathecally to each patient. After the spinals were administered, patients were placed supine with a left tilt. Hypotension was defined as SBP < 75% baseline value, SBP below 90 mmHg, or DBP < 60 mmHg. The authors determined that SBP, MAP, and HR values were increased in the intervention group compared to the control group. Additionally, less

vasopressors were required in the intervention group; ephedrine was administered to 58% of patients in the control group versus 30% of patients in the intervention group (p. 205-209).

Sahoo, SenDasgupta, Goswami, & Harza (2012) looked at parturient patients undergoing cesarean section as well, using a control group (n = 26) and an intervention group (n = 26) which received 4 mg ondansetron prior to the SAB. All patients were pre-loaded with lactated ringers 20 ml/kg/h over 30 minutes. The spinal was established using 2 mL 0.5% bupivacaine (10 mg) and a left tilt was applied post-block. Hypotension was defined as SBP < 90 mmHg or DBP < 60 mmHg. Significant MAP decreases were observed in both groups. In the intervention group, the lowest average mean arterial pressure was 82 mmHg compared to 74 mmHg in the control group. Additionally, 42% of control group patients required phenylephrine administration versus 7.6% of intervention group patients. (p. 24-28).

Ortiz-Gomez et al. (2014) examined 128 parturients who underwent cesarean section. The subjects were divided into four equal groups; a control group, and three study groups which received different doses of ondansetron (2 mg, 4 mg, & 8 mg) prior to SAB. The dose of hyperbaric bupivacaine 0.5% was administered based on height (height in cm X 0.06), and 20 mcg fentanyl was added to each. The authors found no significant difference in the incidence of hypotension. They did, however, find that the study groups which received 4 mg and 8 mg of ondansetron required about half as much ephedrine to correct hypotension (p. 138-143).

Marciniak et al. (2015) studied 72 patients undergoing cesarean section. The study cohort was split into two groups, a control group and an intervention group in which each patient received 8 mg ondansetron five minutes before administration of the spinal. Each patient was preloaded with Hetastarch 10 ml/kg. Bupivacaine 0.5% was administered according to height (1.8-2.2 ml; 9-11mg). Fentanyl 15 mcg was added to each spinal preparation. Post-block, every

patient was positioned supine with a left tilt. Hypotension was defined as a 20% decrease in SBP or SBP < 90 mmHg. The authors determined that were no significant differences in hemodynamic parameters between each group (p. 461-467).

Karacaer et al. (2017) examined prophylactic intravenous ondansetron and its effect on norepinephrine consumption in patients undergoing cesarean section. A total of 108 patients were split evenly into a control group and an intervention group, which received 8 mg ondansetron intravenously prior to receiving the spinal. Co-loading with LR was done, and each patient was administered 10 mg bupivacaine, and 20 mcg fentanyl intrathecally. After the spinal administration, all patients were placed supine with a left tilt. Hypotension was defined as SBP < 80% of the patient's baseline value. The authors determined that incidence of hypotension was statistically equal between groups (88% versus 87%), however, norepinephrine consumption was greater in the control group. In this group, 35.7 +/- 25.8 mcg of norepinephrine was required, versus the intervention group where 22.6 +/- 19.5 mcg of norepinephrine was used (90-97).

A study by Nivatpumin & Thamvittayakul (2016) compared the effectiveness of ondansetron and ephedrine using the respective intervention groups (ondansetron 8 mg, ephedrine 10 mg), as well as a control group. One hundred and sixty-eight patients were enrolled. Each patient was pre-loaded with 500 ml LR, and a spinal was delivered with 11 mg bupivacaine and 200 mcg morphine. The study medications (ephedrine or ondansetron) were given after administration of the spinal. Each patient was also placed supine with left tilt at this time. Hypotension was defined as SBP < 90 or SBP decrease of 20% or greater. The authors determined that "the proportions requiring ephedrine and/or norepinephrine after spinal anesthesia in group [ephedrine] and [ondansetron] were not significantly different" (p. 27) and that the incidence of hypotension was not significantly different between groups (25-31).

Wang et al. (2014) looked at the effectiveness of ondansetron preloading coupled with crystalloid infusion to reduce maternal hypotension after spinal anesthesia for cesarean sections. A control group was compared with an intervention group which received 4 mg ondansetron prior to the delivery of the spinal anesthetic. All patients were given 2 mL of 0.5% (10 mg) bupivacaine and were bolused with 10 mL/kg Lactated Ringer's solution. Hypotension was defined as SBP < 80% baseline and was treated with phenylephrine. The study showed a mean maximal decline in SBP of 18.9 +/- 6.3 mmHg in the group which received ondansetron and 30.7 +/- 16.6 mmHg in the control group. This was determined to be statistically significant. Phenylephrine administration was also significantly different with the intervention group receiving a total of 1,300 mcg and the control group receiving 3,100 mcg in total (p. 913-922).

Non-Obstetric Populations

Marashi, Soltani-Omid, Mohammadi, Aghajani, & Movafegh (2014) completed a study that compared administration of ondansetron in two doses (6 mg and 12 mg) to a placebo dose of saline. Two hundred and ten patients in varying procedures (urologic, orthopedic, and gynecological) were divided into three groups; a control group which received saline, a group which received ondansetron 6 mg, and a group which received ondansetron 12 mg prior to administering the SAB. Hyperbaric 0.5% bupivacaine 15 mg was used for the block. They defined hypotension as a MAP < 80 mmHg and their findings illustrate that only patients in the control group (17%) developed hypotension. This was determined to be of statistical significance. The authors did not indicate how each patient population was distributed to each study group (p.1-5).

Owczuk et al. (2008) compared 35 patients in a control group to 36 patients who received 8 mg ondansetron prior to SAB. No specific population of patients was identified, only that they

all received spinal anesthesia. No preloading of fluids was done prior to the procedure. In fact, each patient was limited to 200 ml sodium chloride during the study period. Each patient received oral midazolam (7.5 mg) one hour prior to anesthesia. Four ml bupivacaine 0.5% (20 mg) was administered intrathecally to each patient. Hypotension was defined as SBP < 90 mmHg. They determined a significant difference between groups in development of hypotension; 20% of patients in the control group versus 2.7% of patients in the intervention group developed hypotension (p.332-339).

Owczuk et al. (2015) examined 53 patients all greater than 70 years of age. The control group had 27 patients and was compared to 26 patients in an intervention group which received 8 mg ondansetron five minutes before SAB. Fluids were limited to 200 ml or less during the study period. Each patient was given 2.5 to 3 ml 0.5% bupivacaine (12.5 – 15 mg) intrathecally. Hypotension was defined as SBP < 90 mmHg, or a SBP decrease of > 20% baseline value. The authors determined that in the intervention group, SBP was significantly higher five minutes after the block was established, and that MAP and DBP were significantly higher at post-block intervals of 5, 10, and 15 minutes (p.598-607).

Article Review Discussion

There have been many studies looking at how intravenous ondansetron affects hemodynamics after the administration of spinal anesthesia. Unfortunately, there exists a large variation in how these studies were conducted. Perhaps the most noteworthy differences include amount and dose of local anesthetic used, adjunct medications used in the spinals, the use of colloid or crystalloid pre- or co-loading, definitions of hypotension, the threshold for treating blood pressure, patient populations and demographics, and dose of ondansetron used.

Of the 13 studies reviewed, eight determined that pre-treating with intravenous ondansetron did reduce the incidence of resultant hypotension. Five of the studies determined that the incidence of hypotension was the same between treatment and control groups. While not all the studies addressed the amount of vasopressor medications used, seven cited that patients who were pretreated with ondansetron required less. Only one cited that the vasopressor load was the same between study groups.

An additional barrier in determining the true effectiveness of this intervention, is that there are many factors that could contribute to the development of hypotension (not exclusively sympathectomy from spinal anesthesia). Some of these factors include, but are not limited to, the administration of Pitocin, which can cause transient hypotension if rapidly infused, the use of propofol infusions, which inhibits sympathetic vasoconstrictor activity, and metabolic byproducts that may accumulate if a tourniquet is used (Butterworth, Mackey, & Wasnick, 2013).

Practice Recommendations

There remains a need for additional, more uniform studies on this topic. Though likely it will be impossible to abolish all variations that exist between the studies, if some of the variables are eliminated, a more determinant conclusion could be reached on the effectiveness of this intervention. Until then, it does seem prudent to administer 4 mg ondansetron intravenously about five minutes prior to administering spinal anesthesia. The reasons for this conclusion include a lack of risk and adverse effects of this dose, the potential for decreasing hypotension, which does have negative consequences, and the likelihood of using a decreased amount of vasopressor medication, which is cost saving. Most of these patients will receive ondansetron during the procedure anyway, so there is no additional cost of this practice. It is important,

however, that each anesthesia practitioner uses case-to-case judgement. It should be realized that this practice cannot fully replace the current strategies of mitigating spinal-induced hypotension, but should rather be looked at as an additional strategy to be used in conjunction with the tools that already exist (fluid loading, positioning, etc.).

References

Brunton, L.L., Hilal-Dandan, R., & Knollmann, B.C. (2018). *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (13th ed.). New York, NY: McGraw-Hill Education.

Butterworth, J.F., Mackey, D.C., & Wasnick, J.D. (2013). *Morgan & Mikhail's Clinical Anesthesiology* (5th ed.). New York, NY: McGraw-Hill Education.

El Khouly, N.I., & Meligy, A.M. (2016). Randomized controlled trial comparing ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during cesarean delivery in Egypt. *International Journal of Gynecology and Obstetrics, 135*(2016), 205-209. doi: 10.1016/j.ijgo.2016.06.012.

Hines, R.L., & Marschall, K.E. (2012). *Stoelting's Anesthesia and Co-Existing Disease* (6th ed.). Philadelphia, PA: Saunders, Elsevier Inc.

Karacaer, F., Biricik, E., Unal, I., Buyukkurt, S., & Unlugenc, H. (2017). Does prophylactic ondansetron reduce norepinephrine consumption in patients undergoing cesarean section with spinal anesthesia? *Journal of Anesthesia 32*(1), 90-97. doi: 10.1007/s00540-017-2436-x

Lee, J.E., George, R.B., & Habib, A.S. (2016). Spinal-induced hypotension: Incidence, mechanisms, prophylaxis, and management: Summarizing 20 years of research. *Best Practice & Research Clinical Anesthesiology 31*(2017), 57-68. doi: 10.1016/j.bpa.2017.01.001

Marashi, S.M., Soltani-Omid, S., Mohammadi, S.S., Aghajani, Y., & Movafegh, A. Comparing two different doses of intravenous ondansetron with placebo on attenuation of spinal-

induced hypotension and shivering. *Anesthesia and Pain Medicine, 4*(2), 1-5. doi: 10.5812/aapm.12055

Marciniak, A., Owczuk, R., Wujtewicz, M., Preis, K., & Majdylo, K. (2015). The influence of intravenous ondansetron on maternal haemodynamics after spinal anaesthesia for caesarean section: a double-blind, placebo-controlled study. *Ginekologia Polska, 2015*(86), 461-467. doi: 10.17772/gp/2405

Matt Vargo. (2012). Vargo Anesthesia Mega App [phone application]. South Carolina.

Nagelhout, J.J., & Plaus, K.L. (2014). *Nurse Anesthesia* (5th ed.). St. Louis, MO: Elsevier, Saunders.

New York School of Regional Anesthesia. (2017). Spinal anesthesia. *Landmark based neuraxial and perineuraxial techniques*. Retrieved from https://www.nysora.com/spinal-anesthesia

Ngan Kee, W.D., Shaw, K.S., & Ng, F.F. (2005). Prevention of hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology, 103*(4), 744-750.

Nivatpumin, P. & Thamvittayakul, V. (2016). Ephedrine versus ondansetron in the prevention of hypotension during cesarean delivery: A randomized, double-blind, placebo-controlled trial. *International Journal of Obstetric Anesthesia, 2016*(27), 25-31. doi: 10.1016/j-ijoa.2016.02.003

Owczuk, R., Wenski, W., Polak-Krzeminska, A., Twardowski, P., Arszulowicz, R., Dylczyk-Sommer, A., Wujtewicz, M.A., Sawicka, W., Morzuch, E. Smietanski, M. & Wujtewicz, M. (2008). Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: A double-blind, placebo-controlled study. *Regional Anesthesia and Pain Medicine, 33*(4), 332-339. doi: 10.1016/j.rapm.2008.01.010

Owczuk, R. Wenski, W., Twardowski, P., Dylczyk-Sommer, A., Sawicka, W., Wujtewicz, M.A., Marciniak, A., Polak-Krzeminska, A., Jasinski, T., Wujtewicz, M. (2015). Ondansetron attenuates the decrease in blood pressure due to spinal anesthesia in the elderly: a double blind, placebo-controlled study. *Minerva Anestesiol, 81*(6), 598-607.

Ortiz-Gomez, J.R., Palacio-Abinzanda, F.J., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jimenez, A., & Bermejo-Albares, M.L. (2014). The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anesthesia: A double-blind, randomized, placebo-controlled trial. *International Journal of Obstetric Anesthesia, 2014*(23), 138-143. doi: 10.1016/j-ijoa.2014.01.005

Sahoo, T., SenDasgupta, C., Goswami, A., & Harza, A. (2012). Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind, randomized, placebo-controlled study. *International Journal of Obstetric Anesthesia, 2012*(21), 24-28. doi: 10.1016/j-ijoa.2011.08.002.

Terkawi, A., Tiouririne, M., Mehta, S.H., Hackworth, J.M., Tsung, S., & Durieux, M.E. (2015). Ondansetron does not attenuate hemodynamic changes in patients undergoing elective cesarean delivery using subarachnoid anesthesia. *American Society of Regional Anesthesia and Pain Medicine, 40*(4), 344-348.

Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M. (2015). Effect of ondansetron on the occurance of hypotension and on neonatal parameters during spinal anesthesia for elective caesarean section: A prospective, randomized, double-blind study. *Anesthesiology Research and Practice 2015*, 1-7. doi: 10.1155/2015/158061

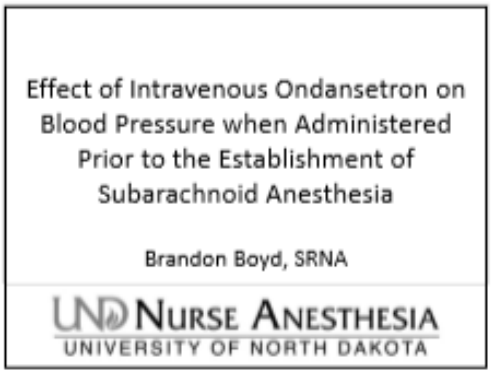
Tubog, T.D., Kane, T.D., & Pugh, M.A. (2017). Effects of ondansetron on attenuating spinal anesthesia-induced hypotension and bradycardia in obstetric and nonobstetric subjects: A systematic review and meta-analysis. *AANA Journal, 85*(2), 113-122.

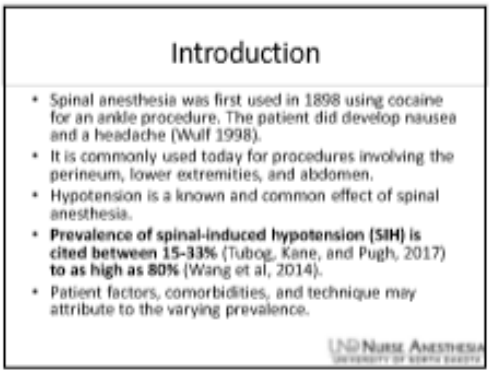
Wang, M. Zhuo, L, Shen, M., Yu, Y., Yu, J., & Wang, M. (2014). Ondansetron preloading with crystalloid infusion reduces maternal hypotension during cesarean delivery. *American Journal of Perinatology, 2014*(31), 913-922. doi: 10.1055/s-0033-1364189.

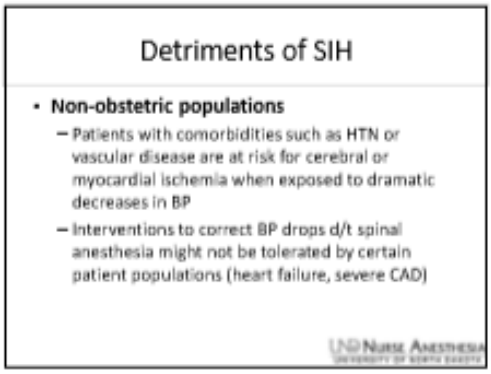
Wang, M., Zhuo, L., Wang, Q., Shen, M., Yu, Y., Yu, J., & Wang, Z. (2014). Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean section delivery: A dose-dependent study. *International Journal of Clinical Experimental Medicine, 7*(12), 5210-5216.

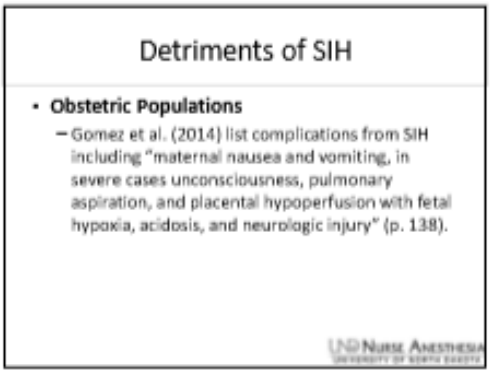
Wulf, H.F.W. (1998). The centennial of spinal anesthesia. *Anesthesiology, 89*(2), 500-506.

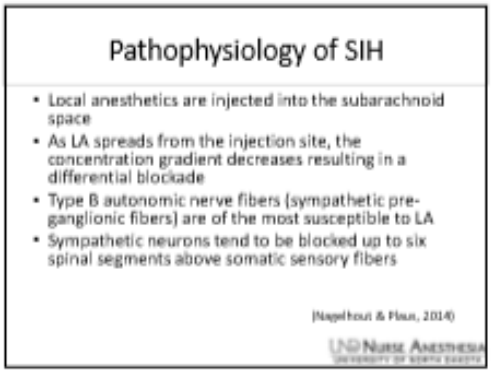
Appendix A

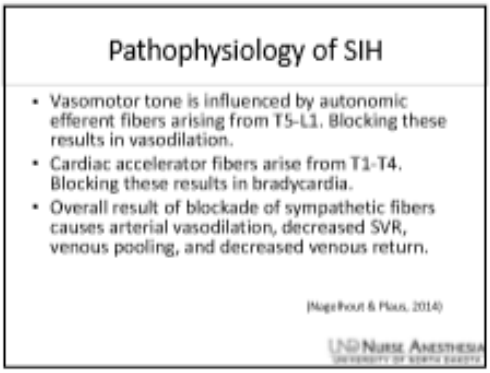












Pathophysiology

- **Bezold-Jarisch Reflex (BJR)**
  - Cardioinhibitory reflex (bradycardia, hypotension)
  - Induced by activation of serotonin (5-HT) receptors (Trebelsi et al, 2017)
  - Serotonin is released in response to hypotension
  - Activation of 5-HT2 receptors located in veins and arteries causes vasoconstriction (Terkawi et al, 2015)
  - Activation of 5-HT3 receptors in cardiac ventricles and on the vagus nerve induces vasodilation and bradycardia (Terkawi et al, 2015)

UND Nurse Anesthesia

Ondansetron

- Serotonin receptor subtype 3 (5-HT3) antagonist.
- Commonly used as an antiemetic as it blocks 5-HT3 receptors in the chemoreceptor trigger zone of the medulla (Vargo Anesthesia, 2012).
- Will also block 5-HT3 receptors peripherally, including those within the cardiac ventricles and on the vagus nerve (Trebelsi et al, 2017).

UND Nurse Anesthesia

Ondansetron Adverse Effects

- Most common include diarrhea, fever, and headache (Butterworth, Mackey, & Wasnick, 2013).
- QT prolongation can occur with 5-HT3 antagonists; more often with dolasetron but, has not been linked clinically to adverse arrhythmias (Butterworth, Mackey, & Wasnick, 2013).
- **Concerns of prenatal adverse effects (spontaneous abortion and development issues)...** Wang et al. (2014) **explored this and determined that ondansetron in appropriate doses is not associated with an increased risk.**

UND Nurse Anesthesia

Case Information

- Total knee arthroplasty
- 64 year-old
- 5'2"
- 72.5 kg
- Female
- ASA 2

UND Nurse Anesthesia

Pre-operative Evaluation

- Past Medical History: Asthma, GERD, HTN
- Surgical History: Tubal ligation, rotator cuff repair, and knee arthroscopy
- No known drug allergies
- Home medications: albuterol, Celebrex 200 mg, gabapentin 100 mg, and hydrochlorothiazide 25 mg
- Pre-op VS: BP 138/84, HR 74, RR 16, SpO2 95%, Temp 98.9 degrees F
- No abnormal pre-op labs or studies
- Airway evaluation was unremarkable

UND Nurse Anesthesia

Anesthetic Course

- Patient received 2 mg midazolam in pre-op
- In OR at 0631; 4 mg ondansetron IV given and 500 mL bolus of LR started
- Patient attached to standard monitoring
- Supine BP 135/85 (101), HR 79, SpO2 100%, RR 14
- Per MDA an additional 6 mg midazolam given
- Patient seated on OR table and spinal administered at 0645 in one atraumatic attempt at L3-4 space
- 1.6 mL bupivacaine 0.75%, and 25 mcg Fentanyl

UND Nurse Anesthesia

Anesthetic Course

- After spinal, patient immediately placed supine and propofol infusion started at 12.5 mcg/kg/min
- Oxygen applied at 3 liters per minute via nasal cannula
- One gram of cefazolin and one gram of tranexamic acid administered
- **First post block BP 109/68 (88), HR 68**
- **Ten minutes post block BP 101/60 (73), HR 68** for which 100 mcg phenylephrine given

UND Nurse Anesthesia

Anesthetic Course

- **This was the only vasopressor dose given**
- Tourniquet up at 0708, incision at 0710
- Throughout SBP ranged from 98-120 mmHg, DBP ranged from 53-68 mmHg.
- Lowest MAP encountered was 68, this was 85 minutes post-SAB and occurred after tourniquet was let down
- HR throughout ranged from 58-80 BPM
- Tourniquet down at 0801 (total time 53 minutes)

UND Nurse Anesthesia

Anesthetic Course

- After tourniquet let down, a second gram of tranexamic acid was given
- Propofol infusion d/c'd at 0813
- Total LR given was 1.2 liters
- EBL 225 ml

UND Nurse Anesthesia

Intraoperative Issues

- Hypotension (relative) for which phenylephrine (100 mcg) given
- Difficulty determining height of block due to amount of midazolam given prior to block administration

UND Nurse Anesthesia

PACU

- Patient to PACU at 0831; BP 108/64, HR 61, SpO2 100%, RR 14
- Surgeon realized he forgot to place subcutaneous sutures and decided to do so in PACU
- 2 additional mg midazolam given to facilitate this
- Patient tolerated well, no complications

UND Nurse Anesthesia

IV Ondansetron to Attenuate SIH

- Reviewed 13 RCTs
- Methods of each study were similar but there is variability between them
- Differences in studies include:
  - Dose of LA
  - Adjunct medications used in the spinals
  - Use of colloid or crystalloid pre- or co-loading
  - Definitions of hypotension & the threshold for treating hypotension
  - Patient populations and demographics
  - Dose of ondansetron

UND Nurse Anesthesia

IV Ondansetron to Attenuate SIH

- **8 of the studies determined pre-treating with IV ondansetron did reduce the incidence of SIH**; 5 determined the incidence was unchanged
- Not all addressed vasopressor doses for correcting SIH; seven of the studies cited that patients who were pretreated with ondansetron required less

UND Nurse Anesthesia

IV Ondansetron to Attenuate SIH

- **Non-Obstetric Populations**
  - Marashi et al. (2014) looked at 3 study groups (70 patients per group), placebo group, 6 mg ondansetron group, and 12 mg ondansetron group.
  - 17% of placebo group developed hypotension (defined as MAP < 80)
  - **No hypotension noted in the intervention groups**
  - Two studies by Owczuk et al. (2008 & 2015) had similar findings with 8 mg doses of ondansetron

UND Nurse Anesthesia

IV Ondansetron to Attenuate SIH

- **Obstetric Populations**
  - Varying results
  - Trabelsi et al. (2015) showed a difference in SIH incidence between a control group (n = 40; **77.5% incidence**) and 4 mg ondansetron intervention group (n = 40; **37.5% incidence**).
  - Ortiz-Gomez et al. (2014) showed no difference in incidence between control group, and three study groups which received 2 mg, 4 mg, and 8 mg ondansetron, respectively. **However, those that received 4 mg and 8 mg ondansetron required half as much ephedrine to treat hypotension.**

UND Nurse Anesthesia

IV Ondansetron to Attenuate SIH

- Another Barrier
  - Almost no studies addressed other factors that can cause hypotension such as:
  - Pitocin administration
  - Propofol infusions
  - Tourniquet use and metabolic byproducts

UND Nurse Anesthesia

Recommendations

- Additional, more uniform, studies should be completed to determine the actual effectiveness of using IV ondansetron to attenuate SIH
- It can be recommended to administer 4 mg ondansetron IV prior to SAB
  - Lack of risk/adverse effects
  - There is potential for diminishing hypotension which carries negative consequences
  - Likelihood of decreasing vasopressor medication use (cost saving)
  - Most of these patients will receive ondansetron during the case anyway (no additional cost)

UND Nurse Anesthesia

Conclusion

- With this recommendation, it needs to be realized that this practice cannot fully replace the current strategies of mitigating SIH (fluid bolus, vasopressors, etc).
- It should be looked at as an additional strategy to be used in conjunction with the tools that already exist.
- Anesthesia providers should use case-to-case judgement

UND Nurse Anesthesia