Ondansetron and Spinal-Induced Hemodynamic Effects: What Anesthesia Providers Should Know

Brittany A. Burke, RN, BSN

Kelly J. Clubb, RN, BSN

Advent Health University

Project Mentor: Dr. David Yui, MD

Project Mentor: Steven St. Onge, PharmD, BCPS, MBA

Project Chair: Manuel Tolosa, CRNA, DNAP

March 22, 2019

Abstract

Ondansetron is a 5-HT3 serotonin antagonist that has been implicated in the attenuation of spinal-induced hypotension and bradycardia. Randomized control trials, systematic reviews, and meta-analysis studies showed that administration of prophylactic ondansetron five minutes prior to the placement of a subarachnoid block, or spinal anesthetic, resulted in a decreased incidence of hypotension and bradycardia among parturients. One of the leading causes of complications during a cesarean section is directly related to the hemodynamic changes seen with a spinal anesthetic. The use of ondansetron can lead to increased patient safety and is a cost-effective measure in maintaining stable hemodynamics. The purpose of this project was to educate student registered nurse anesthetists (SRNAs) attending Advent Health University (AHU) on the benefits of intravenous ondansetron to attenuate spinal-induced hypotension and bradycardia. For discussion purposes, a literature review was conducted by searching multiple databases in which an educational and comprehensive PowerPoint was derived and presented to the SRNAs at AHU. A pre- and posttest consisting of ten multiple-choice questions were disseminated and collected from the twenty-two SRNAs. The data was analyzed and assessed for advancement of knowledge among the students using a paired sample t-test in an SPSS software program. The mean scores increased from pretest (75%) to posttest (97%). The paired samples test results indicated an educational PowerPoint was successful in increasing the knowledge base amongst SRNAs on the use of intravenous ondansetron to attenuate spinal induced hemodynamic effects ($t = -6.087$, $p < .001$). This is pertinent to our practice as implementing ondansetron into a spinal anesthetic plan is crucial to improve patient outcomes and enhance safety.

Table of Contents

Introduction

Spinal anesthesia, also known as neuraxial anesthesia, is a safe and effective method of anesthesia used for a variety of procedures and is common globally among obstetric patients. Benefits of spinal anesthesia include early recovery and mobility, cost effectiveness, decreased use of opioids, reduced frequency of nausea, and better pain control. However, spinal anesthesia comes with adverse side effects including but not limited to hypotension and bradycardia to cardiac and respiratory arrest (Zhou, Zhu, Bao, Wang & Liu, 2018).

The hypotensive effects from spinal anesthesia are attributed to a local anesthetic induced sympathetic blockade, reducing cardiac output, and subsequently blood pressure (Friedly & Simmons, 2015). In spinal anesthesia the height of the block is related to patient positioning. An important physiological change that occurs with pregnancy, aortocaval compression from the gravid uterus, places the obstetric population at a greater risk for spinal-induced hypotension. Gao, Zheng, Han, Wang, and Zheng (2015) noted that 70-80% of obstetric subjects experienced spinal-induced hypotension without pharmacologic interventions. A variety of pharmacological methods ranging from the use of crystalloids and colloids to pre-load or co-load, and the use of intravenous vasopressors including ephedrine and phenylephrine, have been utilized to avoid spinal-induced hypotension. However, the use of vasopressors can have mild to severe detrimental maternal and fetal effects such as bradycardia, fetal hypoxia, and cardiac arrhythmias (Friedly & Simmons, 2015).

While neuraxial anesthesia is beneficial for multiple reasons, the most common initial side effects can cause bradycardia, hypotension, and subsequently, nausea (Baig, Shah, Khurshid, Abid & Tariq, 2017). Recently, studies have shown the use of ondansetron in attenuating the hypotensive and bradycardic effects induced by spinal anesthesia in healthy

obstetric subjects. However, the researchers believed there could be a lack of clinical application of current evidence among anesthesia practitioners, specifically, among student registered nurse anesthetists (SRNAs) with regards to the use of ondansetron to mitigate spinal-induced hypotension and bradycardia. The proposed educational module in the form of a PowerPoint presentation sought to breach that gap between current evidence and clinical practice. Therefore, the purpose of this document was to synthesize research to answer the question: Will the review of literature presented to SRNAs with limited clinical experience demonstrate that in obstetric patients, is the administration of prophylactic intravenous ondansetron effective in attenuating the bradycardic and hypotensive effects of neuraxial anesthesia, if administered prior to placement? Furthermore, this paper will specifically aim to answer the question: in senior SRNAs scheduled to graduate in 2019 enrolled at AHU, will an educational PowerPoint presentation improve the knowledge base regarding the use of prophylactic ondansetron as a pharmacologic intervention to attenuate spinal-induced hypotension and bradycardia?

Literature Review

Neuraxial anesthesia has a rapid onset and has been associated with decreased intraoperative blood loss, reduced transfusion requirements, blockade of surgical stress response, a decreased risk for thromboembolism, and an overall reduction in morbidity and mortality (Baig et al., 2017). Zhou et al. (2018) stated that spinal anesthesia was the preferred anesthetic for cesarean sections due to its simplicity and minimal impact on the fetus. Allowing a mother to remain conscious and pain-free during her birthing process has been shown to improve emotional health, mother-infant bonding, and levels of patient satisfaction. Neuraxial anesthesia also avoids the depressant effects of anesthetic drugs that can negatively impact maternal and fetal well-being. Thus, it is crucial for anesthesia providers to recognize the benefits and risks of

neuraxial anesthesia to optimize patient safety and satisfaction. For the purpose of this review, hypotension was defined as a systolic blood pressure drop greater than 20% baseline, and bradycardia was defined as a heart rate of less than fifty beats per minute (Abbas, Shah, & Naqvi, 2016; Baig et al., 2017; Jarineshin, Fekrat, & Kashani, 2016; Trabelsi et al., 2015; Wang et al., 2014).

To further understand the impact of neuraxial anesthesia on the parturient, a physiological discussion must occur. At term, uteroplacental vessels are dilated to reduce resistance to flow and ensure adequate nutrient delivery to the fetus (Friedly & Simmons, 2015). The parturient may also experience a phenomenon known as aortocaval compression, or supine-hypotension. This is caused by vena cava and abdominal aorta compression by the gravid uterus resulting in a reduction of venous return and cardiac output (Nagelhout & Plaus, 2014). A common method to avoid aortocaval compression is to displace the gravid uterus via positioning the patient with a left lateral tilt. However, according to Nagelhout and Plaus (2014), when spinal anesthesia was used to produce the required T4 dermatome level block, nearly 80% of patients, despite left uterine displacement, experienced hypotension. Therefore, the compounded supine hypotension with neuraxial anesthesia has led to devastating effects such as decreased uteroplacental blood flow, and potentially higher fetal morbidity (Trabelsi et al., 2015). Heesen, Kilmek, Hoeks, and Rossaint (2016) stated that fifty-percent of obstetric patients fell victim to spinal-induced hypotension that led to an increased risk of complications including nausea, vomiting, altered consciousness, and aspiration. Hypotension also contributed to hypoperfusion of the placenta, fetal hypoxia, acidosis, and neurologic injury (Ortiz-Gomez et al., 2014).

Parturients become dependent on sympathetic tone to maintain hemodynamics as pregnancy progresses, which further compounds the effects seen from administration of spinal

anesthesia. In order to ensure that an adequate sensory blockade has been reached to tolerate the cesarean section, a thoracic dermatome 4 (T4) block is required. This level, although beneficial for patient comfort, plays a crucial role in the blockade of sympathetic outflow that causes the deleterious effects such as spinal-induced hypotension and bradycardia.

Several studies explained the sympathectomy produced by injection of local anesthetics into the subarachnoid space. The blockade of sympathetic outflow at the T4 level leads to peripheral and central vasodilation, and therefore, a decreased venous return to the heart. This then resulted in decreased systemic vascular resistance and preload secondary to vasodilation (Heesen et al., 2016; Gao et al., 2015; Ortiz-Gomez et al., 2014). Tubog, Kane, and Pugh (2017) further explained that the venous system contributes up to 75% of our total blood volume. Systemic vasodilation thus resulted in venous pooling and a reduction in venous return.

The bradycardic effect of spinal anesthesia has recently been attributed to stimulation of serotonin receptors in the ventricle wall, which elicit a cardioinhibitory reflex, known as the Benzold Jarnish Reflex, or BJR (Heesen et al., 2016; Baig et al., 2017; Zhou et al. 2018; Jarineshin et al. 2016). According to Heesen et al. (2016), decreased venous return to the right heart stimulates the receptors within the heart wall and was presumed to be the culprit for the initiation of the BJR. The activation of the BJR leads to a shift that allows the parasympathetic nervous system to become dominant. Stimulation of peripheral serotonin receptors, as well as the mechano- and chemoreceptors activated by the parasympathetic nervous system located in the heart wall, caused bradycardia, hypotension, and cardiovascular collapse via non-myelinated C-fibers (Tubog et al., 2017). The hemodynamic effects that occur due to the BJR can be detrimental in patients who may be unable to improve venous return by increasing their heart

rate. In the obstetric population particularly, such hemodynamic effects can significantly impact maternal and fetal well-being, and result in an emergent situation.

The goal in obstetric patients who have received spinal anesthesia should be to optimize the patient to prevent and effectively treat hypotension before complications arise. Research has implicated multiple techniques in an effort to understand and prevent issues. Gao et al. (2015) discussed other concomitant methods to reduce the spinal-induced hemodynamic effects such as the use of intravenous fluids, positioning, vasopressor drugs, and lower-leg pneumatic compression devices. Unfortunately, no single technique has been confirmed to effectively treat the spinal-induced phenomena that occur.

Current scientific research has revealed the use of phenylephrine and ephedrine to prevent and treat spinal-induced hypotension (Gao et al., 2015; Heesen et al., 2016). Conversely, Friedly & Simmons (2015) explained that the use of phenylephrine and ephedrine was implicated to reduce uteroplacental perfusion and contribute to fetal acidosis. The use of colloids and vasopressors was also a factor in the development of anaphylaxis, impaired coagulation, and cardiac dysrhythmias (Friedly & Simmons, 2015). Finally, pneumatic compression devices on lower extremities are known to improve venous return. However, the pneumatic compression devices were reported to potentially lead to lower extremity ischemia and patient discomfort (Friedly & Simmons, 2015). Thus, despite the multiple tactics to improve patient safety, risks apply and necessitate the need for further research into safe and effective treatment options.

Ondansetron is a 5-HT3 serotonin receptor antagonist that is commonly used in practice as an antiemetic (Nagelhout & Plaus, 2014). It produces its effects on peripheral receptors located in the cardiac vagal afferents and centrally on receptors in the chemoreceptor trigger zone (Tubog et al., 2017). Due to the locations of its target receptors, ondansetron is useful in

preventing nausea, hypotension, and bradycardia. Studies also suggested a decrease in the use of vasopressors, as ondansetron assisted in mitigating the hypotensive effects of spinal anesthesia (Gao et al., 2015; Ortiz-Gomez et al., 2014; Heesen et al., 2016). Gao et al. (2015) found when ondansetron was given prophylactically five minutes prior to the spinal anesthetic, the use of both ephedrine and phenylephrine to treat bradycardia and hypotension were significantly reduced. Rather than focusing on the maternal hypotensive effects of prophylactic administration of ondansetron, Ortiz-Gomez et al. (2014) focused on the change in arterial pressure to project the influence on maternal hemodynamics. Ortiz-Gomez et al. (2014) found a significant dose-dependent reduction in the use of ephedrine when prophylactic ondansetron was administered five minutes prior to spinal anesthesia. In the meta-analysis conducted by Heesen et al. (2016), the use of ephedrine and phenylephrine to treat spinal-induced hypotension was significantly reduced when a 5-HT3 antagonist, such as ondansetron, was administered prior to the spinal anesthetic. Although rare and less severe, side effects of ondansetron include headache, constipation, diarrhea, QT interval prolongation, and somnolence (Wang et al., 2014; Nagelhout & Plaus, 2014). However, the benefits of the use of prophylactic ondansetron outweigh the risks of the pharmacologic side effects (Zhou et al., 2018).

Based on the previously stated information about ondansetron, spinal-induced hypotension and BJR research studies have been conducted in an effort to link the administration of ondansetron to the attenuation of spinal-induced hypotension and bradycardia. Wang et al. (2014) concluded that prophylactic administration of 4mg and 6mg doses of ondansetron five minutes prior to spinal anesthesia significantly reduced the incidence of maternal hypotension. This study also concluded that the use of 2mg or 8mg doses of ondansetron pre-loading had no benefit to the parturient in reducing maternal hypotension (Wang et al., 2014). Jarineshin et al.

(2016) conducted research on ondansetron but also included a 500mL lactated ringer bolus prior to the anesthetic and procedure. The research was similar to Wang et al. (2014) with pre-loading of ondansetron five minutes prior to the placement of the spinal anesthetic. The research found that the use of ondansetron in combination with a crystalloid preload significantly prevented the reduction in diastolic blood pressure and mean arterial pressure (Wang et al., 2014). This study did not, however, find a correlation between intravenous ondansetron without crystalloid preload and the prevention of bradycardia (Wang et al., 2014). Additional research conducted has implicated that the use of ondansetron in comparison to a placebo results in significantly lower incidences of bradycardia but did not show any statistical significance regarding hypotension (Zhou et al., 2018).

Although there was presence of conflicting research, the consensus presided that the use of ondansetron was a safe and cost-effective mechanism in reducing the incidence of spinal-induced hypotension and bradycardia (Abbas et al., 2016; Baig et al., 2017; Gao et al., 2015; Heesen et al., 2016; Tubog et al., 2017; Wang et al., 2014; Zhou et al., 2018). Based on the literature review conducted, eight of the eleven articles found the use of prophylactic ondansetron to be effective in the reduction of spinal-induced hypotension and bradycardia. The methods to the studies varied with different dosages of ondansetron in combination with the use of preloading with crystalloid. Ortiz-Gomez et al. (2014) found that the use of ondansetron was insignificant in the reduction of spinal-induced hypotension and bradycardia. Ortiz-Gomez et al. (2014) instead proposed that the choice of local anesthetic used was an important contributing factor to spinal-induced hemodynamic effects. In contrast, Jarineshin et al. (2016) found that the use of intravenous ondansetron had little effect on the prevention of a decrease in systolic blood pressure and heart rate, however, was effective in preventing a reduced diastolic blood pressure

and mean arterial pressure. The systematic review protocol proposal by Friedly & Simmons (2015) did not provide any synthesis of outcomes after administration of ondansetron but provided valuable information regarding the physiology and implications of spinal-induced hypotension and bradycardia.

It is of our opinion that there is an adequate amount of evidence to evaluate the effectiveness of ondansetron to reduce hypotension and bradycardia, however, the minimal effective dose warrants further investigation. There was presence of research implicating the effective dose; however, the use of ondansetron has not become a standard of care. A more comprehensive study of minimum effective dose, if proven to support the use of ondansetron, could warrant changes in future standards of care that would require every anesthesia provider to incorporate this into their practice. In the interest of discussing limitations, this topic was limited in its available research population. Common themes among studies conducted were the exclusion of any parturient with co-existing diseases, multiparity, hypertensive disorders, or any other history that would not allow the patient to be classified as an American Society of Anesthesiologists (ASA) grade one or two. Although in the interest of clear data collection this exclusion was understandable, it is with this specific patient demographic that providers need to be more cognizant of adverse events secondary to spinal anesthesia. A subset of this research that focused on parturients with a more detailed history would be beneficial to include all obstetric patients, rather than simply healthy parturients without comorbidities.

Contribution and Dissemination / Justification

With hypotension occurring in 50-80% of obstetric patients who receive neuraxial anesthesia, it was critical to educate future anesthetists of safe and effective methods to prevent and treat the hypotension and bradycardia to avoid adverse outcomes. This project was meant to

synthesize data collected within the previous five years, to provide evidence-based information to incorporate the administration of ondansetron to the obstetric population to attenuate spinal-induced hypotension and bradycardia. This project intended to make future practitioners aware of the pathophysiologic causes of spinal-induced hypotension and bradycardia and to expand the knowledge base of drug interactions, mechanisms of action, and physiological effects of ondansetron in obstetric patients. The target population consisted of twenty-three graduate level student nurse anesthetists enrolled at Adventist University of Health Sciences in the Nurse Anesthesia Program. These students have had a sound background of pharmacology, anatomy and physiology, and the physiological changes that occur in obstetric patients. The SRNAs were presented with an educational PowerPoint presentation on September 13, 2018. The effectiveness of the educational PowerPoint was determined by a pre- and posttest, as evidence by an increase in scores.

Project Aims

The aim of this project was to educate future anesthesia practitioners on the effectiveness of intravenous ondansetron on the attenuation of spinal-induced hypotension and bradycardia. In other words, the primary goal of this project was to improve SRNA's knowledge base and expand pharmacologic interventions outside of vasopressors for spinal-induced hypotension and bradycardia. Currently, SRNAs have had a sound knowledge base of vasopressors and appropriate dosages to treat hypotension. After giving an educational presentation, we projected an increase in the median scores between the pretest and posttest. An increase in scores would imply an effective PowerPoint presentation and an increase in the SRNAs knowledge base regarding ondansetron to attenuate spinal-induced hypotension and bradycardia.

Project Methods

The projected design of this project was a quantitative study amongst our fellow peers. After obtaining approval from ADU's Scientific Review Committee, SRC, and Institutional Review Committee, IRB, a pretest and a posttest was administered to evaluate the effectiveness of a forty-minute PowerPoint presentation meant to enhance SRNA's knowledge base in the use of ondansetron to attenuate spinal-induced hypotension and bradycardia. The PowerPoint presentation consisted of basic information, research studies that proved the effectiveness of ondansetron, and critical-thinking questions to engage our audience into discussion. Our target population consisted of twenty-three of our classmates at Adventist University of Health Sciences enrolled in the nurse anesthesia program. Each participant was required to sign an informed consent, and complete a pretest prior to the presentation. Any SRNA who refused to sign an informed consent, arrived late to class, or had any competing interest with the use of ondansetron was excluded from this quantitative evaluation. However, there were no students excluded from this educational module. Once completed, the posttest was collected prior to the participants leaving the room. The researchers didn't place any personal identifying information on the tests to ensure confidentiality. There were ten multiple choice questions. Once the tests were received, there was a review of the answers and results among the researchers. Using a personal computer that was password protected, the results were saved in a safe location. All paper documents were locked in a filing cabinet in which only the authors of this project, Brittany Burke and Kelly Clubb, had access to. The data collected was sent to Adventist University's Research Department to Roy Lukman, statistically analyzed the data using a SPSS computer software program. A paired sample t-test was used to interpret the data and a p-value of < 0.05 was considered statistically significant. Within three weeks of the presentation, analyzed data was available. The data is planned to be disseminated during our research day via

poster display. Once the project was completed, all electronic documents were deleted, and all paper documents were placed in a locked shred bin set to be destroyed.

Project Timeline

The work proposed to complete this project was conducted across the span of three academic trimesters. The first trimester occurred during the summer from May until August 2018. The timeline of tasks in the summer trimester included creation of a topic, a thorough literature review with synthesis, and a written scholarly project proposal to be submitted to our committee chair and project mentors by May 28, 2018. CITI modules required to carry out our scholarly project were completed and submitted by May 30, 2018. Revisions of our scholarly project proposal draft were completed and submitted to our project chair and mentors by June 14, 2018. A draft of the application for submission to the IRB/SRC was submitted to our project chair by June 29, 2018. Included in the IRB/SRC application were the development of a pretest and posttest, director site approval letter, and informed consent. Upon revision, the application was officially submitted to the research office via ADU's web-based research project submission process by July 17, 2018. Investigators received summary of the SRC review by August 6, 2018. Following SRC review, the research office submitted the scholarly project proposal to the IRB and notified the investigators of the IRB summary by September 12, 2018. The MSNA 690 course faculty assigned September 13, 2018 for the researchers to present the PowerPoint presentation and collect the pre-and posttest examinations on that same date. Data collection and implementation was then initiated on the same day at the conclusion of the group presentation. Thereafter, post-implementation data was collected and analyzed within three weeks of the completed presentation date. Dissemination of our results will be announced in April of 2019 with our poster presentation.

Data Collection Plan

On the scheduled presentation day, the researchers arrived prior to the participants to ensure all materials were available to be disseminated among the participants. Each participant was introduced to the informed consent. It was required that each participant sign an informed consent and it was collected prior to the start of the presentation. The ten multiple choice questions assessed the key points of the presentation. The researchers ensured that the answers to the questions were included in the presentation to maintain integrity of the educational information presented. These questions were presented via identical pre- and posttest, clearly labeled, to assess the effectiveness of the educational PowerPoint presentation. The two researchers distributed and instructed each participant to complete the pretest and submit it to the researchers prior to the initiation of the presentation. The researchers then ensured that the tests received were pretests prior to proceeding, and that the number of pretests collected corresponded to the number of participants. This eliminated the risk of a participant completing multiple pretests. The presentation then began and once completed, the researchers distributed the posttest to the participants. Again, the researchers proceeded to collect and count the tests to ensure that only posttests, and the appropriate amount was received. Thus, there was a total of six exchanges between the researchers and participants. These exchanges included handing each participant the informed consent, receiving the informed consent from each participant, handing the pretest to each participant, collection of each pretest, handing the posttest to each participant, and finally, collection of each posttest.

Evaluation Plan

The intended goal of this scholarly project was to educate and inform Adventist University's student registered nurse anesthetists on the use of intravenous ondansetron in the

attenuation of spinal-induced hypotension and bradycardia. This project included an educational presentation with a pre- and posttest evaluation process. This allowed for the researchers to assess their level of knowledge prior to and after an educational PowerPoint presentation. Data was collected and compiled using an Excel spreadsheet. Once the data was collected, it was sent to the designated person to interpret the data. The projected computer software used for analysis was a SPSS program. The data was analyzed using a paired sample t-test. Once analyzed, anything that represents a p-value of < 0.05 was considered significant. Results that were deemed significant were evidenced by an increase in the mean score between the pre- and posttest.

Results and Findings

The researchers graded the pretests and posttests and sent the results to Dr. Roy Lukman for additional statistical analysis. A paired sample t-test was utilized via an SPSS program to analyze the data. The mean scores increased from pretest scores averaging at 75% to posttest scores averaging 97%. The paired samples test results indicated an educational PowerPoint was successful in increasing the knowledge base amongst SRNAs on the use of intravenous ondansetron to attenuate spinal induced hemodynamic effects ($t = -6.087$, $p < .001$). The negative result from the t-value indicates that the mean posttest scores significantly increased from the mean pretest scores. The comprehensive statistical analysis is summarized in a chart format in appendix D.

Conclusion and Limitations

In conclusion, this project has shown to prove that an educational PowerPoint presentation was successful in increasing the knowledge base of SRNAs regarding the use of ondansetron to attenuate spinal-induced hemodynamic effects.

Limitations projected for our study included our audience, a homogenous sample, as all participants were student registered nurse anesthetists enrolled in Adventist University of Health Sciences. Additionally, our convenience sample size, n=22, was limited. No participant arrived late, refused to partake in this project, or left early from the presentation, which could have diminished our sample size and caused further study limitations. All participants had completed multiple courses in pharmacology, which may have skewed data via artificial enhancement of knowledge. Thus, the small sample size and previous education on ondansetron may have falsely elevated or hindered our results. The use of a PowerPoint presentation provided a limitation in the utilization of different learning and delivery styles of the content presented. Lastly, the presentation took place in one sitting over the course of forty minutes. Since there was not a long time-lapse between the educational PowerPoint presentation and the posttest, the retention of knowledge could not be reliably assessed. The pre- and posttest were created to validate the improvement of scores based on the educational module only.

Despite the limitations listed above, the researchers completed the PowerPoint presentation and the results from the paired sample t-test revealed a significant improvement in the pre- and posttest scores. This led the researchers to believe that the educational PowerPoint presentation was effective in improving the SRNA's knowledge base. The overall score improved by 22.273%, which implied that the SRNA's were receptive to the PowerPoint and learned from it. The pretest scores surprised the researchers, however, as they were higher than expected. This topic was not previously discussed in didactic coursework, and the researchers expected lower scores than were achieved. Nonetheless, each student has experienced clinical practicum that may have previously exposed them to this topic.

Although the data validated an increase in knowledge base among the SRNA's, it cannot be determined what the future implications of this educational module will be. The use of ondansetron has not become a standard of care, and it was discussed that individual preference was the main factor in the incorporation of ondansetron into care. The researchers were satisfied with the results and hope that in the future ondansetron will be used for the purpose of reducing hemodynamic effects induced by a spinal anesthetic.

References

Abbas, N., Shah, S., Naqvi, S. (2016). Role of prophylactic ondansetron for prevention of spinal anaesthesia induced hypotension in lower segment caesarean section. *Pakistan Armed Forces Medical Journal, 66*(6), 790-794. Retrieved from www.pafmj.org/

Baig, R., Shah, A. A., Khurshid, T., Abid, L., & Tariq, Z. (2017). Use of ondansetron for prevention of spinal induced hypotension. *Journal of Islamabad Medical & Dental College, 6*(4), 208-213. Retrieved from https://jimdc.org.pk/

Friedly, C. & Simmons, S. (2015). Prophylactic ondansetron for prevention of maternal hypotension following spinal anesthesia in women undergoing cesarean section: A systematic review protocol. *JBI Database of Systematic Reviews & Implementation Reports,* 13(9), 84-94. https://doi.org/10.11124/jbisrir-2015-2373

Gao, L., Zheng, G., Han, J., Wang, Y., & Zheng, J. (2015). Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: A meta-analysis. *International Journal of Obstetric Anesthesia, 4*(24), 335-343. https://doi.org/10.1016/j.ijoa.2015.08.012

Heesen, M., Kilmek, M., Hoeks, S. E., & Rossaint, R. (2016). Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptan receptor antagonists: A systematic review and meta-anaylsis and meta-regression. *Anesthesia and Analgesia, 123*(4), 977-988. https://doi.org/10.1213/ANE.0000000000001511

Jarineshin, H., Fekrat, F., & Kashani, S. (2016). Effect of ondansetron in prevention of spinal anesthesia-induced hypotension in pregnant women candidate for elective cesarean section. *Journal of Current Research in Science, 4*(1), 57-62. Retrieved from www.jcrs010.com/

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

Saunders.

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

Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M. (2015). Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anesthesia for elective cesarean section: A prospective, randomized, controlled, double blind study. *Anesthesiology Research and Practice.* https://doi.org/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. *American Association of Nurse Anesthetists, 85*(2), 113-122. Retrieved from http://www.aana.com/newsandjournal

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 delivery: a dose-dependent study. *International Journal of Clinical and Experimental Medicine, 7*(12), 5210-5216. Retrieved from www.ijcem.com/

Zhou, C., Zhu, Y., Bao, Z., Wang, X., & Liu, Q. (2018). Efficacy of ondansetron for spinal anesthesia during cesarean section: A meta-analysis of randomized trials. *Journal of International Medical Research, 46*(2), 654-662. https://doi.org/10.1177/0300060517716502

Appendix A

AHU NAP CAPSTONE PROJECT – INFORMED CONSENT

This scholarly project is being performed by two private investigators, MSNA students, in the Nurse Anesthesia Program (NAP) at Advent Health University (AHU). We are doing a Capstone Project called *Ondansetron and Spinal-Induced Hemodynamic Effects: What Anesthesia Providers Should Know*. This project is being supervised by a nurse anesthesia faculty member. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to educate the 2019 student registered nurse anesthetist cohort enrolled at Advent Health University regarding evidenced-based practice in the use of ondansetron to attenuate the hypotensive and bradycardic effects of spinal anesthesia.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

Your participation in this study is voluntary. You may choose to not to participate. The decision to participate or not participate in this research study is completely up to you. If you choose not to participate your refusal to participate in this research study will involve no penalty or loss of benefits to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw informed the PI of your wishes.

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address the mechanism of action of local anesthetics used for spinals, the mechanism of action of ondansetron, physiological changes in obstetric patients, hemodynamic changes related to spinal anesthesia, adverse events due to spinal anesthesia, and methods utilized to prevent and/or treat spinal-induced hypotension and bradycardia. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately forty minutes.

You do not have to participate in this research study and choosing not to participate in this study will not involve any penalty or loss of benefit to you. The decision to participate or not participate in this research study is completely up to you. If you choose to participate, you can change your mind later and withdraw your consent and discontinue participation from this study at any time. If you chose to withdraw from the study informed the PI of your wishes.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the AHU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about pharmacological interventions such as the use of ondansetron to attenuate spinal-induced hypotension and bradycardia.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. Participants will remain anonymous through the use of a numbering system. Pre- and posttests will be distributed in an envelope at random to the twenty-three participants. All information will be collected and stored securely by the researchers and will only be seen by the researchers, the project chair, the project mentors, and the designated statistician at AHU. The data will be destroyed upon completion of the project. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately forty minutes of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ **Date** _____

Participant Signature/ Participant Name(SIGNED LEGIBLY)

_____**Participant Name (PRINTED LEGIBLY)**

Appendix B

Pretest and Posttest

1. What are the most common side effects from neuraxial anesthesia?
    a. Hypotension
    b. Bradycardia
    c. Hypertension
    d. Both A and B

2. What reflex is associated to hypotension?
    a. Bainbridge Reflex
    b. Benzold-Jarnish Reflex
    c. Baroreceptor Reflex
    d. Autonomic hyperreflexia

3. The use of vasopressors to treat maternal hypotension can result in which of the following adverse events?
    a. Fetal hypoxia
    b. Maternal arrhythmias
    c. Maternal bradycardia
    d. All of the above

4. Physiologic changes during pregnancy include which of the following?
    a. Increased estimated blood volume
    b. Increased cardiac output
    c. Supine hypotension
    d. All of the above

5. Pressure from a gravid uterus compressing the abdominal aorta and vena cava is known as?
    a. Supine hypertension
    b. Aortocaval syndrome
    c. Baroreceptor Reflex
    d. Fetal hypoxia

6. Which of the following best describes the mechanism of action of ondansetron?
    a. 5-HT3 serotonin receptor antagonist on peripheral receptors located on the cardiac vagal afferents and central receptors in the chemoreceptor trigger zone
    b. GABA-A agonist that allowed increased conductance of chloride to depolarize a cell
    c. Binds to μ-receptor via Gi protein to inhibit Adenylyl cyclase leading to decreased Ca^{++} influx to cytoplasm & efflux from sarcoplasmic reticulum
    d. Binds with the muscarinic cholinergic receptors to prevent acetylcholine from attaching to the receptor sites

7. Other methods used to reduce spinal-induced hypotension and bradycardia include which of the following?
    a. Pneumatic compression devices on the lower extremities
    b. Preloading with crystalloid and/or colloid
    c. Vasopressors
    d. All of the above

8. Hypotension occurs in what percent of the obstetric population due to neuraxial anesthesia?
    a. 10-20%
    b. 30-40%
    c. 50-80%
    d. 100%

9. Injection of a local anesthetic into the subarachnoid space for an elective cesarean section results in which of the following effects?
    a. Hypotension due to sympathetic block at the thoracic dermatome T4 resulting in peripheral and central vasodilation, decreased systemic vascular resistance, and decreased preload
    b. Hypertension due to sympathetic block at the thoracic dermatome T4 resulting in peripheral and central vasoconstriction, increased systemic vascular resistance, and increased preload
    c. Hypotension due to parasympathetic block at the thoracic dermatome T4 resulting in peripheral and central vasodilation, decreased systemic vascular resistance, and decreased preload
    d. Hypertension due to parasympathetic block at the thoracic dermatome T4 resulting in peripheral and central vasoconstriction, increased systemic vascular resistance, and increased preload

10. Obstetric patients mainly rely on what system to maintain hemodynamics throughout pregnancy?
    a. Parasympathetic nervous system
    b. Cardiovascular system
    c. Sympathetic nervous system
    d. Central nervous system

*correct answers in bold font

Appendix C

PowerPoint Presentation

ONDANSETRON AND SPINAL-INDUCED HEMODYNAMIC EFFECTS: WHAT ANESTHESIA PROVIDERS SHOULD KNOW

Brittany A. Burke
Kelly J. Clubb
Project Mentor: Dr. David Yui, MD
Project mentor: Steven St. Onge, PharmD, BCPS, MBA
Project chair: Manuel Tolosa, CRNA, DNAP

Objectives

- Discuss physiological changes during pregnancy
- Discuss alternative methods to attenuate spinal-induced hemodynamic effects
- Discuss the pathophysiologic causes of spinal-induced hypotension (SIH) and bradycardia
- Discuss the mechanism of action and benefits to administration of intravenous ondansetron prior to administration of a spinal anesthetic
- Improve SRNA's knowledge base and expand pharmacologic interventions outside of vasopressors to treat spinal-induced hemodynamic effects

Case Study

- Patient: 28 year old female
- Surgical Procedure: primary cesarean section
- H&P: Healthy primigravida, 40 weeks today. No prior history.
- Scenario: Upon spinal administration, the patient complained of nausea and dizziness. The CRNA immediately treats with multiple aggressive doses of phenylephrine and ephedrine. The blood pressure returned a reading of 74/45 and the HR was 52. After 15 minutes, fetal tracings showed non-reassuring signs of compromise resulting in obstetrician converting the case to an emergency. APGARs for the baby were 4 at 1 minute and 7 at 5 minutes. Admitted to NICU for observation.

Background of Problem

- Globally, cesarean deliveries account for 33% of births and 1 million procedures annually (Friedly & Simmons, 2015)
- Neuraxial anesthesia is common and carries less of a risk than general anesthesia
- **50-80% of obstetric patients experience hypotension after neuraxial anesthesia without pharmacologic interventions**
- Physiologic changes with pregnancy further contribute to hemodynamic changes
- Potential harm to mother and/or fetus

PICOT Question # 1

- Will the review of literature presented to SRNAs with limited clinical experience demonstrate that in obstetric patients, is the administration of prophylactic intravenous ondansetron effective in attenuating the bradycardic and hypotensive effects of neuraxial anesthesia, if administered prior to placement?

PICOT Question # 2

- In senior SRNAs scheduled to graduate in 2019 enrolled at ADU, will an educational PowerPoint presentation improve the knowledge base regarding the use of prophylactic ondansetron as a pharmacologic intervention to attenuate spinal-induced hypotension and bradycardia?

Motivation and Goals

- Enhance knowledge of pharmacotherapy amongst future nurse anesthetists to prevent spinal-induced hemodynamic effects
- **With hypotension occurring in 50-80% of obstetric patients who receive neuraxial anesthesia**, it is critical to educate future anesthetists of safe and effective methods to prevent and treat the hypotension and bradycardia to avoid adverse outcomes.
- Provide evidence-based information on the administration of ondansetron to successfully attenuate spinal-induced hypotension and bradycardia

LITERATURE REVIEW

Neuraxial Anesthesia

Benefits

- Safe and effective
- Higher fetal APGAR scores vs. general anesthesia
- Reduced maternal morbidity and mortality
- Predictable and rapid recovery
- Provides a rapid onset of a dense blockade

Drawbacks

- Bradycardia
- Hypotension
- Nausea and vomiting
- Limited duration of anesthesia
- Limited ability to titrate extent of sensory blockade (T4 = sympathectomy)

(Nagelhout & Plaus, 2014; Abbas, et al., 2016; Baig et al., 2017; Jarineshin, et al., 2016; Trabelsi et al., 2015; Wang et al., 2014)

Normal Physiologic Changes With Pregnancy

- **Increased Estimated Blood volume and cardiac output** (Nagelhout & Plaus, 2014)
- Increased oxygen consumption
- Increased levels of progesterone beginning at 8-12 weeks
  - Increases sensitivity to local anesthetics
  - Increases nitric oxide leading to vasodilation
  - Decreases the response to angiotensin and norepinephrine
- **Aortocaval compression: gravid uterus causes compression to the aorta and inferior vena cava** (Nagelhout & Plaus, 2014)
  - Can decrease CO by 30% compromising fetal perfusion
  - Displace uterus via left lateral tilt position

(Friedly & Simmons, 2015; Nagelhout & Plaus, 2014; Trabelsi et al., 2015)

Physiologic Changes With Pregnancy That Further Contribute to SIH

- At term, uteroplacental vessels are maximally dilated and results in low resistance and lack of autoregulation in response to low blood pressure (Friedly & Simmons, 2015)
- **Parturients become dependent on sympathetic tone to maintain hemodynamic stability as pregnancy progresses**
  - T4 blockade leads to enhanced effects from SIH and bradycardia
- Fasting for elective cesarean section leading to dehydration and low preoperative blood volumes

Uteroplacental Blood Flow

- Essential for delivery of oxygen and nutrients to the fetus
  - -Chronic reduction leads to fetal growth restriction (Nagelhout & Plaus, 2014)
- Causes of decreased uterine blood flow include:
  - -Decreased uterine arterial pressure
    - Supine position
    - Hemorrhage
    - Drug-induced hypotension
    - Hypotension during sympathetic blockade (Friedly & Simmons, 2015)

Uteroplacental Blood Flow

- Causes of decreased uterine blood flow include:
  - Increased uterine venous pressure
    - Uterine contractions
  - Increased uterine vascular resistance
    - Endogenous vasoconstrictors
      - Catecholamines from stress response
      - Vasopressin in response to hypovolemia
    - Exogenous vasoconstrictors
      - Epinephrine, vasopressors, and local anesthetics in high concentrations

(Nagelhout & Plaus, 2014)

Uteroplacental Blood Flow

- In relation to neuraxial anesthesia
  - Increase uterine blood flow due to:
    - pain relief, decreased sympathetic activity, and decreased maternal hyperventilation (Friedly & Simmons, 2015)
  - Decreased uterine blood flow due to:
    - hypotension, unintentional IV injection of local anesthetic and/or epinephrine, and absorbed local anesthetic (Nagelhout & Plaus, 2014)

Physiology of Spinal Anesthesia

- Local anesthetics exert their effects at multiple sites within spinal cord and nerve roots
- The primary site of local anesthetic action is on the myelinated preganglionic fibers of the spinal nerve roots
- Results in an interruption of neural transmission of posterior and anterior nerve root fibers
  - Posterior: visceral and somatic sensation
  - Anterior: inhibition of efferent motor and autonomic outflow
  - Sodium channel inhibition which stops an action potential from firing

(Nagelhout & Plaus, 2014)

Local Anesthetics and Pregnancy

- Spread and depth of spinal and epidural anesthesia are increased in pregnant women
  - Decreased thoracolumbar cerebrospinal fluid (CSF)
    - Engorged veins compress the subarachnoid space reduces dose requirement
  - Hormonal changes
    - Presence of progesterone in CSF
      - Increases neural sensitivity to local anesthetics

(Nagelhout & Plaus, 2014)

Complications of Subarachnoid Blocks

- **Most common**
  - **Hypotension**
  - **Bradycardia**
- Nausea / Vomiting
  - Related to the rapid onset of hypotension and parasympathetic stimulation of the GI tract
- Post-dural puncture headache
- High motor neuronal blockade / altered consciousness
- SIH and bradycardia, if left untreated, can quickly progress to cardiac arrest.

(Nagelhout & Plaus, 2014; Zhou et al., 2018; Wang et al., 2014; Abbas et al., 2016)

Spinal-Induced Hypotension

- The sum effects of neuraxial anesthesia on the cardiovascular system depends on the degree of sympathetic blockade in terms of rostral spread of the anesthetic and partially on the degree of patient sedation and central sympathetic inhibition.
- **Blockade of the sympathetic nervous system causes arterial vasodilation, decreased systemic vascular resistance, venous pooling, and a reduction in venous return.**
- If block is high enough, the sympathetic nerve fibers that innervate the heart, cardiac accelerators (T1-T4) become anesthetized
  - Imbalance between vagal fibers further slows heart rate
- Baroreceptor reflexes, volume receptor reflexes, and decreased central sympathetic outflow all contribute to the complexity of the cardiovascular response to neuraxial anesthesia

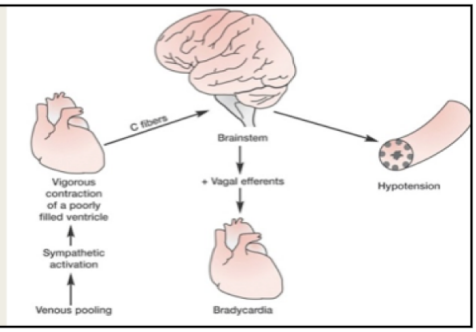
(Heesen et al., 2016; Baig et al., 2017; Zhou et al. 2018;Jarineshin et al. 2016).

Benzold-Jarisch Reflex (BJR)

- **A triad of bradycardia, hypotension, and vasodilation in response to cardiac receptor stimulation**
- Decreased filling to right atrium reduces outflow of intrinsic chronotropic stretch mechanoreceptors in ventricle wall
- Serotonin receptors within ventricle wall become stimulated, leading to cardioinhibitory reflex
- Parasympathetic nervous system becomes dominant, leading to vasovagal response
- Typically, these are self-limited, however in the presence of a sympathectomy can cause cardiac collapse

(Heesen et al., 2016)

BJR



(Heesen et al., 2016)

Preventative Management of BJR & SIH

- **Intravenous fluids at 10-15 mL/kg preload or co-load**
- **Positioning**
- **Vasopressors**
- Ephedrine vs. phenylephrine
- **Lower-leg pneumatic compression devices**
- No single effective technique

(Gao et al., 2015; Nagelhout & Plaus, 2014; Zhou et al., 2018)

Shortcomings of Preventative Treatment

- **Use of ephedrine and phenylephrine to treat SIH**
  - **Reduced uteroplacental perfusion**
  - **Fetal acidosis**
  - **Maternal arrhythmias**
- Colloid and vasopressor use:
  - Implicated in development of anaphylaxis, impaired coagulation and cardiac dysrhythmias
- Pneumatic compression devices:
  - Known to improve venous return, however, can cause lower extremity ischemia and patient discomfort

(Friedly & Simmons, 2015; Nagelhout & Plaus, 2014; Zhou et al., 2018; Gao et al., 2015)

Ondansetron

- **5-HT3 serotonin receptor antagonist**
- **Works on peripheral receptors located in the cardiac vagal afferents and centrally in the chemoreceptor trigger zone**
- Blocks the Benzold-Jarisch reflex (BJR)
- Useful in preventing nausea, hypotension, and bradycardia
- Decreases the use of vasopressors (Gao et al., 2015; Ortiz et al., 2014; Heesen et al., 2016)
- Potential side effects: headache, constipation, diarrhea, QT interval prolongation and somnolence (Wang et al., 2014; Nagelhout & Plaus, 2014)

Study Criteria

- Hypotension is defined as a systolic blood pressure reduction greater than 20% of baseline, and bradycardia as a heart rate less than fifty beats per minute (Abbas et al., 2016; Baig et al., 2017; Jarineshin et al., 2016; Trabelsi et al., 2015; Wang et al., 2014)
- Parturients were selected based on age and health (Abbas et al, 2016; Baig et al., 2017; Jarineshin et al., 2016; Ortiz et al., 2014; Trabelsi et al., 2015; Wang et al., 2014)
- ASA class 1 & 2 (no significant differences)
- All variables were recorded: age, height, BMI, intraoperative timing, SBP, DBP, MAP, HR, oxygen saturation
- Any side effects that occurred were recorded: nausea & vomiting, skin flushing, discomfort, need for vasopressor & initial/final hemoglobin levels
- Hemodynamic variables were recorded before administration of ondansetron, then 2 minute intervals for 15 minutes, and then 5 minute intervals after

Effects on Ondansetron Attenuating Hypotension

Authors	Date of Article	Significant Results	Significance Level
Abbas, N., Shah, S., Naqvi, S.	2016	Ondansetron 4 mg administered. 42% experienced SIH in ondansetron group, while 68% experienced in placebo group.	$P = 0.009$
Baig, R., Shah, A. A., Khurshid, T., Abid, L., & Tariq, Z.	2017	6 mg ondansetron administered. Hypotension in obstetric placebo group was 28.3%, while ondansetron group experienced 7.5% hypotension. No significance in non-obstetrics.	$P = 0.005$
Gao, L., Zheng, G., Han, J., Wang, Y., & Zheng, J.	2015	Prophylactic treatment of intravenous ondansetron in both obstetric and non-obstetric patients reduce the incidence of hypotension.	Hypotension: $p = 0.0005$
Tarineshin, H., Fekrat, F., & Kashani, S.	2016	Ondansetron 4 mg diluted into 500mL normal saline bolus prevented reduction in DBP and MAP, with no significance in SBP (p=0.08) or heart rate (p=0.31) within an hour of receiving the spinal	MAP: $p = 0.01$ DBP: $p = 0.01$

Effects on Ondansetron Attenuating Hypotension

Authors	Date of Article	Significant Results	Significance Level
Ortiz-Gomez, J. R., Palacio-Abizanda, F. J., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jimenez, A., & Bermejo-Albares, M. L.	2014	Higher doses of ondansetron, 8 mg compared to 2 and 4 mg doses, decreased the hypotensive effects of spinal anesthesia in women having a caesarean delivery.	$P = 0.04$
Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M.	2015	Ondansetron had significant effect on the incidence of hypotension in healthy patients undergoing caesarean delivery with spinal anesthesia.	$P < 0.001$
Tubog, T. D., Kane, T. D., & Pugh, M. A.	2017	Spinal-induced hypotension was reduced 36%. Doses of 4mg ondansetron reduced hypotension by 22%, however, there was no significant data amongst groups who received 6 mg, 8 mg, and 12 mg of ondansetron.	$P < 0.001$
Wang, M., Zhao, L., Wang, Q., Shen, M., Yu, Y., Yu, J., & Wang, Z.	2014	Incidence of SIH reduced in 4mg and 6mg groups, no statistical difference in 2 mg and 8 mg doses. SBP, DBP, MAP & HR significantly higher in 6 mg dose.	$P < 0.05$

Effects of Ondansetron on Bradycardia

Authors	Date of Article	Significant Results	Significance Level
Abbas, N., Shah, S., Naqvi, S.	2016	Administration of 4 mg of Ondansetron reduced the incidence of bradycardia	$P = 0.026$
Heesen, M., Kilmek, M., Hoeks, S. E., & Rossaint, R.	2016	Incidence of bradycardia was significantly lower in subject who received 5-HT3 antagonist	$P = 0.01$
Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M.	2015	Bradycardia was noted less in the Ondansetron group than the placebo group.	$P = 0.02$
Tubog, T. D., Kane, T. D., & Pugh, M. A.	2017	Treatment with ondansetron reduced the risk of bradycardia 69%.	$P < 0.001$
Wang, M., Zhao, L., Wang, Q., Shen, M., Yu, Y., Yu, J., & Wang, Z.	2014	No bradycardia noted in Ondansetron groups that received 4 mg, 6 mg and 8 mg.	$P < 0.03$
Zhou, C., Zhu, Y., Bao, Z., Wang, X., Liu, Q	2018	Ondansetron had a significant effect on reducing the incidence of bradycardia	$P = 0.006$

Effects of Ondansetron on Need for Vasopressors

Authors	Date of Article	Significant Results	Significance Level
Heesen, M., Kilmek, M., Hoeks, S. E., & Rossaint, R.	2016	5-HT3 antagonists significantly reduced the amount of vasopressor needed for the treatment of hypotension	P 0.0003
Gao, L., Zheng, G., Han, J., Wang, Y., & Zheng, J.	2015	Prophylactic treatment of intravenous ondansetron in both obstetric and non-obstetric patients reduce the requirement for vasopressor use.	Vasopressor use: $p <$ 0.05
Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M.	2015	Due to the less frequent incidence of hypotension, the group receiving Ondansetron required significantly less ephedrine intraoperatively.	$P < 0.001$
Wang, M., Zhao, L., Wang, Q., Shen, M., Yu, Y., Yu, J., & Wang, Z.	2014	The consumption of phenylephrine was significantly lower in the 4mg ondansetron group than the placebo group.	$P = 0.05$

Research Limitations

- Anesthetic Technique
  - Technique and dose are considerable factors leading to differences among studies
- Personalizing spinal dosing, rather than a "blanket dose"
- What leads to the high variance of incidence of SIH?
  - If 50-80% of patients will experience it, what is the cause of this varying incidence?
- Provider experience with recognition and treatment varies

Research Limitations

- Minimal effective dose has been debated, a further discussion would be beneficial
- No standard of care adopted to include ondansetron administration
- Limited available research population
- Parturients included in the study were healthy ASA 1 with no co-existing diseases
  - A more comprehensive assessment with parturients with a more detailed history would be an important addition
- Ondansetron is on national shortage, and thus, may not be readily available at facilities

Implication to Practice

- Ondansetron comes with minimal detrimental side effects and is a safe additional method to counteract the BJR
- No single intervention has been proven to completely counteract the BJR, so a multimodal approach is key
- The use of ondansetron is not considered the standard of care
- The administration has been most effective 5 minutes prior to placement
- Give once the patient is sitting for spinal or upon entering the operating room

Conclusion

- Current evidence suggests that prophylactic ondansetron has a role in attenuating hypotension and bradycardia after subarachnoid anesthesia in healthy obstetric patients
- Decreases in DBP, MAP, and vasopressor requirements were significantly lower in parturients receiving prophylactic ondansetron compared to placebo
- Several studies found statistically significant differences in heart rate between ondansetron and placebo groups
- No single concomitant technique proven to effectively treat spinal-induced hemodynamic effects
- Added benefit for it's mechanism of action in preventing nausea and maternal and fetal safety profile

References

Abbas, N., Shah, S., Naqvi, S. (2016). Role of prophylactic ondansetron for prevention of spinal anaesthesia induced hypotension in lower segment caesarean section. *Pakistan Armed Forces Medical Journal, 66*(6), 790-794. Retrieved from www.pafmj.org/

Baig, R., Shah, A. A., Khurshid, T., Abid, L., & Tariq, Z. (2017). Use of ondansetron for prevention of spinal induced hypotension. *Journal of Islamabad Medical & Dental College, 6*(4), 208-213. Retrieved from https://jimdc.org.pk/

Friedly, C. & Simmons, S. (2015). Prophylactic ondansetron for prevention of maternal hypotension following spinal anesthesia in women undergoing cesarean section: A systematic review protocol. *JBI Database of Systematic Reviews & Implementation Reports,* 13(9), 84-94. https://doi.org/10.11124/jbisrir-2015-2373

Gao, L., Zheng, G., Han, J., Wang, Y., & Zheng, J. (2015). Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: A meta-analysis. *International Journal of Obstetric Anesthesia, 4*(24), 335-343. https://doi.org/10.1016/j.ijoa.2015.08.012

Heesen, M., Kilmek, M., Hoeks, S. E., & Rossaint, R. (2016). Prevention of spinal anesthesia-induced hypotension during cesarean delivery by 5-hydroxytryptan receptor antagonists: A systematic review and meta-anaylsis and meta-regression. *Anesthesia and Analgesia, 123*(4), 977-988. https://doi.org/10.1213/ANE.0000000000001511

Jarineshin, H., Fekrat, F., & Kashani, S. (2016). Effect of ondansetron in prevention of spinal anesthesia-induced hypotension in pregnant women candidate for elective cesarean section. *Journal of Current Research in Science, 4*(1), 57-62. Retrieved from www.jcrs010.com/

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

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

Trabelsi, W., Romdhani, C., Elaskri, H., Sammoud, W., Bensalah, M., Labbene, I., & Ferjani, M. (2015). Effect of ondansetron on the occurrence of hypotension and on neonatal parameters during spinal anesthesia for elective cesarean section: A prospective, randomized, controlled, double blind study. *Anesthesiology Research and Practice.* https://doi.org/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. *American Association of Nurse Anesthetists, 85*(2), 113-122. Retrieved from http://www.aana.com/newsandjournal

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 delivery: a dose-dependent study. *International Journal of Clinical and Experimental Medicine, 7*(12), 5210-5216. Retrieved from www.ijcem.com/

Zhou, C., Zhu, Y., Bao, Z., Wang, X., & Liu, Q. (2018). Efficacy of ondansetron for spinal anesthesia during cesarean section: A meta-analysis of randomized trials. *Journal of International Medical Research, 46*(2), 654-662. https://doi.org/10.1177/0300060517716502

Appendix D

Results Analysis Chart

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PreTest	75.0000	22	17.92843	3.82235
	PostTest	97.2727	22	4.55842	.97186

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTest - PostTest	-22.27273	17.16359	3.65929	-29.88264	-14.66282	-6.087	21	.000

The paired samples t test was conducted to analyze your data. The obtained t value (-6.087) is associated with $p < .001$ which is statistically significant. It, therefore, can be concluded that the average percentage scores significantly increased between pretest (75.00%, sd=17.93%) to posttest (97.27%, sd=4.56%). It is also interesting to note that the standard deviation for the posttest scores is much less than Pretest, which indicates that there is much less variance in the posttest scores.