Ondansetron before spinal anesthesia in cesarean sections: An evidence-based educational intervention

Madison Jimison

Marian University

Leighton School of Nursing

Chair: Dr. Derrianne Monteiro

_____
(Signature)

Project Team Members: Dr. Adrienne Merrick

_____
(Signature)

Date of Submission: 03/13/2023

Table of Contents

Abstract

Background and Review of Literature: Spinal anesthesia is the current gold standard of practice for providing care in elective cesarean sections. However, spinal anesthesia is commonly associated with untoward side effects including activating the Bezold-Jarisch reflex leading to significant hypotension and bradycardia. Current evidence-based literature shows the administration of a 5-HT3 antagonist, such as intravenous Zofran, can reduce these side effects as well as reduce the amount of vasopressors used to provide optimal patient care.

Purpose: This study explored the efficacy of an educational intervention on increasing the willingness and knowledge to utilize a 5-HT3 antagonist before a spinal anesthetic in cesarean sections

Methods: An email list of 25 active anesthesia providers at a large metropolitan hospital was acquired and presented the educational opportunity via email. This included a Qualtrics pre-educational questionnaire, an attached educational PowerPoint, and a Qualtrics post-educational questionnaire. These helped to determine current anesthetic practices, basic knowledge of Zofran, and willingness to adopt a 5-HT3 antagonist into anesthetic practices before spinal anesthesia.

Implications/Conclusion: The implementation of an educational intervention on eight anesthesia providers significantly increased education and knowledge. Alternatively, the educational intervention did not significantly increase willingness to change anesthetic practices due to the high *extremely willing* response rate in the pre-educational questionnaire.

Keywords: ondansetron, Zofran, 5-HT3 antagonist, spinal anesthesia, subarachnoid block, cesarean sections, blood pressure, hemodynamics, hypotension

Ondansetron before spinal anesthesia in cesarean sections: An evidence-based educational intervention

Introduction

Spinal anesthesia is a vital component for providing adequate and satisfactory care for cesarean sections. However, a spinal anesthetic is commonly associated with activating the Bezold-Jarisch reflex which contributes to significant hypotension and bradycardia (Tatikonda et al., 2019). This can cause untoward effects on both the mother and the baby. Recent studies have shown significant prevention of spinal-induced side effects when a 5-hydroxytryptamine 3 (5-HT3) antagonist, such as ondansetron (Zofran) is administered before the procedure. Proper formation and implementation of an educational intervention that includes the discussion of intravenous (IV) Zofran before performing a spinal anesthetic can optimally increase anesthesia providers use which can further improve patient outcomes, reduce vasopressor use, and reduce care costs.

Background

Spinal anesthesia first dates to 1885 when cocaine was injected into the spinous process of the lumbar area to produce loss of sensation (Marx, 1994). Since then, it has been effective in a variety of procedures and preferred for its avoidance in airway manipulation, adverse effects of certain general anesthetic drugs, improved postoperative pain, and reduced postoperative opioid requirements (Stewart et al., 2020). However, spinal anesthesia is not free from unfavorable side effects or considerations since it is associated with physiologic changes of the central nervous system, cardiovascular system, respiratory system, and gastrointestinal system (Nagelhout & Elisha, 2018). Specifically, spinal anesthesia blocks sympathetic nerve transmission that results in arterial vasodilation, decreased systemic vascular resistance, venous pooling, and reduction in

venous return that occurs in up to 75% of cases (Šklebar, 2019). Furthermore, the Bezold-Jarisch reflex is activated with an abrupt autonomic withdrawal of sympathetic response and increased vagal tone. The combination of increased venous pooling and increased vagal tone may result in profound hypotension and bradycardia that can be challenging to rapidly treat or reverse (Nagelhout & Elisha, 2018).

Hypotension prevents perfusion to critical organs in the body such as the heart and brain and is important in maintaining homeostasis. Maternal hypotension results in problematic nausea and vomiting and if severe, may result in decreased level of consciousness, aspiration of gastric contents, and cardiovascular collapse (Nagelhout & Elisha, 2018). Detrimental neonatal effects such as fetal acidosis and death may develop with uteroplacental hypoperfusion (Aksoy et al., 2021). The goal is to rapidly treat hypotension in this patient population before further complications arise.

Multiple strategies have been identified for optimal treatment of spinal-induced hypotension. Researchers have focused on the prevention of spinal-induced hypotension by targeting the effects of the Bezold-Jarisch reflex. It is concluded that serotonin and 5-HT3 receptors in the heart, lung, and spine are responsible for the activation of this reflex (Aksoy et al., 2021). Several studies have shown that by administering a 5-HT3 antagonist such as intravenous ondansetron (Zofran) before spinal anesthesia, it can attenuate hypotension and inhibit peripheral vasodilation, easing the Bezold-Jarisch reflex, and increasing venous return, ultimately leading to decreased side effects and vasopressor usage (Nivatpumin & Thamvittayakul, 2016).

Problem Statement

Hypotension is a common and problematic complication that is commonly associated with spinal anesthesia. It can produce detrimental effects on both the laboring mother and her baby. Many studies have shown the benefit of administering Zofran, a 5-HT3 antagonist, before performing the procedure to reduce the incidence of hypotension and its associated issues (Nivatpumin & Thamvittayakul, 2016). However, not all health care facilities or anesthesia providers routinely administer IV Zofran before spinals in cesarean sections. This project explored the efficacy of an educational intervention on increasing the willingness and knowledge to utilize a 5-HT3 antagonist before a spinal anesthetic in cesarean sections.

Needs Assessment and Gap Analysis

The site for this project is a health care organization that commonly performs cesarean sections. This facility demonstrated administration of IV Zofran before spinal anesthesia is not a common practice in cesarean sections. The lack of education and knowledge of IV Zofran offers an opportunity to implement an educational intervention that will optimally improve anesthesia providers willingness to adopt IV Zofran into their routine anesthetic techniques and improve knowledge on the subject.

Literature Review

Methods

A comprehensive literature review was performed regarding the effects of administering IV 5-HT3 antagonist before spinal anesthesia in cesarean sections. The process aimed to include articles with IV 5-HT3 antagonist, such as ondansetron, as the primary intervention and its effects on hemodynamics. A comprehensive search was performed on Pubmed and CINAHL databases using primary terms and Boolean phrases including *ondansetron OR Zofran OR 5-HT3 antagonist, spinal OR spinal anesthesia OR subarachnoid block, cesarean sections OR c-section,*

blood pressure OR hemodynamics OR hypotension. Exclusion criteria was applied to ensure the results included literature from the years 2015 or newer, were able to be read in English, human trials, peer-reviewed, randomized-control trial, clinical trial, or retrospective study.

The search process uncovered 60 articles that were further screened for review. Further exclusion criteria were applied that limited the articles to pregnant women, 5-HT3 antagonist as primary intervention, effects on hemodynamics, and elective cesarean sections. This returned a total of 17 articles that are included in this review.

Results

Of the 17 articles included in this review (see appendix D), 11 articles advocated for the use of prophylactic Zofran as it reduced spinal-induced hypotension and/or decreased the amount of vasopressors that were used to control hypotension (Aksoy et al., 2021; Chatterjee et al., 2020; El Khouly & Meligy, 2016; Karacaer et al., 2017; Nivatpumin & Thamvittayakul, 2016; Ortiz-Gomez et al., 2017; Phipps, 2016; Qian et al., 2020; Tatikonda et al., 2019; Wang et al., 2014; Xiao et al., 2019). Several factors were measured throughout the different studies but the main variables of vital signs, vasopressor use, and adverse outcomes were consistent. Two studies (Aksoy et al., 2021; Chatterjee et al., 2020), specifically studied the effectiveness of Granisetron, a 5-HT3 antagonist like ondansetron, and its effects on hemodynamics. A combined total of 320 participants were examined and both studies advocated for the use of Granisetron, and the effectiveness of decreasing blood pressure shifts and reducing the use of vasopressors, specifically ephedrine and mephentermine. Wang et al. (2014), determined that IV Zofran before spinal anesthesia significantly decreases spinal-induced hypotension as well as improved nausea and vomiting, improved acid-base balance in the newborn, and a reduced vasopressor requirement. While the study of El Khouly & Meligy (2016), demonstrated that IV Zofran

significantly decreased blood pressure and heart rate fluctuations while also reducing the incidence of nausea and vomiting.

Multiple studies examined vasopressor requirements to maintain blood pressure after spinal anesthesia. Although hemodynamics was not significantly different for patients given IV Zofran before their spinal, many studies found that vasopressor requirements were significantly reduced (Alghanem et al., 2020; Karacaer et al., 2017; Nivatpumin & Thamvittayakul, 2016; Phipps, 2016; Qian et al., 2020; Tatikonda et al., 2019; Xiao et al., 2019). Xiao et al. (2019), found that 4 mg of IV Zofran reduced the ED50 (dose required to produce a desired pharmacologic effect in 50% of the population) of phenylephrine infusions by 26%. While Karacaer (2017), confirmed that hypotensive events and phenylephrine requirements were higher in the normal saline control group compared to the group who received 8mg of Zofran prophylactically. Furthermore, the study of Ortiz-Gomez et al. (2017), concluded 8mg of Zofran before spinal anesthesia decreases the severity of hypotension, leading to an overall reduction of hypotensive events by 50% per patient.

Additional findings of a prophylactic 5-HT3 antagonist before spinal anesthesia in cesareans sections include decreased episodes of shivering, and decreased antiemetic requirements (Tatikonda et al., 2019)(Oofuvong et al., 2018). Qian et al. (2020), also demonstrated 4mg ondansetron given 15 minutes before a spinal offers no additional benefits than 4mg ondansetron given 5 minutes before a spinal.

Of the 17 articles, four determined IV ondansetron offered no benefit to decrease the episodes of hypotension in cesarean sections (Marciniak et al., 2015; Neumann et al., 2020; Oofuvong et al., 2018; Terkawi et al., 2015). Terkawi et al. (2015), also found that ondansetron does not reduce nausea and vomiting, pruritis, or vasopressor consumption. Additionally, one

study found 25mg intramuscular (IM) of ephedrine 25 minutes before spinal anesthesia contributed to the best prevention of systolic blood pressure changes when compared to 4mg of ondansetron (Ranjbar et al., 2018).

Theoretical Framework

The Iowa Model of Evidence-Based Practice to Promote Quality Care served as the theoretical framework for this project (see Appendix A). This model focuses on identifying clinical need and translating evidence-based research into clinical practices. When analyzing this model, it was identified that underutilization of intravenous Zofran is the clinical problem addressed. The literature review identified the well documented research behind the use of Zofran before spinal anesthesia. The model suggests that if sufficient research is available in favor of the practice change, then the introduction of practice change should be pursued. This theoretical framework is relevant to this project as it proposed an educational intervention to increase the administration of an intravenous 5-HT3 antagonist before spinal anesthesia to help reduce or prevent spinal hypotension and vasopressor use in cesarean sections as demonstrated in current literature.

Project Aims and Objectives

The overall goal of this project was to implement an educational intervention based on current evidence-based practices to increase the knowledge and willingness to implement IV Zofran before performing spinal anesthesia in elective cesarean sections. In turn, this will reduce a myriad of problems that are commonly associated with spinal anesthesia during cesarean sections such as bradycardia, hypotension, and fetal compromise (Aksoy et al., 2021). The education intervention included certified registered nurse anesthetists (CRNA) who commonly perform elective cesarean sections. The main objectives were to first assess the basic knowledge

of anesthesia providers and their current practices regarding spinal anesthesia in cesarean sections. A lack of knowledge of the benefits of IV Zofran contributes to decreased administration and decreased compliance. After a baseline knowledge was established, an educational intervention was implemented, and a post-educational questionnaire expectantly improved provider knowledge and increase provider willingness to perform spinal anesthesia after a 5-HT3 antagonist.

Project Design/Methods

This project was best suited for an educational intervention. Educational interventions have been shown to significantly improve health care workers knowledge, skills, and understanding of key concepts when compared to other interventions (Cusack et al., 2018). Since the objective of this study was to increase the understanding and utilization of a 5-HT3 antagonist before spinal anesthesia, an educational intervention will expectantly improve this outcome.

An online educational opportunity was created using evidence-based research to promote best practice guidelines. A pre-test established a baseline in Zofran (or any other 5-HT3 antagonist) utilization, knowledge on the pharmacology of these drugs, as well as any hesitations or concerns on the effectiveness of Zofran before a spinal anesthetic. A PowerPoint presentation was then used to provide education and a post-test determined the effectiveness of the educational intervention on knowledge, as well as willingness to include a 5-HT3 antagonist before a spinal anesthetic in cesarean sections.

Project site and population

The project was implemented online via email to anesthesia providers employed within a large, metropolitan hospital with over 320 staffed hospital beds. This inner-city hospital has the

largest number of births per year in Indiana from the years 2014-2020, with a yearly average of about 4,000 births (Community Health Network, 2020). Anesthesia providers, including certified registered nurse anesthetists (CRNA) employed at this hospital will be invited to participate in this project.

Methods

This project was created with the aid of Qualtrics and PowerPoint. First, a list of all active anesthesia providers was obtained by the current chief of anesthesia at the project site. Next, a self-created pre-educational questionnaire was created. It was composed of 12 questions to determine demographics, current anesthetic practices, basic knowledge of Zofran, willingness to give a 5-HT3 antagonist before spinal anesthesia, and personal hesitations on giving a 5-HT3 antagonist before spinal anesthesia (see appendix C).

Next, a PowerPoint presentation was responsible for the available education. The PowerPoint included detailed information about the use of a 5-HT3 antagonist (Zofran) in spinal anesthetics for cesarean sections, basic pharmacology of Zofran, synopsis of the review of literature explained above, and benefits of administering Zofran before a spinal.

Lastly, a self-created post-educational questionnaire was included. The questionnaire focused on increased knowledge and willingness to include Zofran in future anesthetic practices. It was composed of five questions that matched the pre-educational questionnaire exactly (see appendix D). Both the pre- and post-educational questionnaire were validated via Marian faculty and CRNAs.

Both the pre- and post-educational questionnaires were included in a composed email as links to the Qualtrics website. The questionnaires were by invitation only and were only allowed to be taken once per participant. The PowerPoint presentation was also included as an

attachment. The steps were listed in numerical for easy completion. The project materials remained available for two and a half weeks and a reminder email was sent halfway through the allotted time. After closing of the project, a statistical analysis was performed to determine the effectiveness of the educational intervention and willingness to include a 5-HT3 antagonist into personal spinal anesthesia practices. A Likert Scale was used for majority of the questions asked during both surveys to establish strength of an attitude in linear fashion. The questionnaires were anonymous, and participation was voluntary.

Data Collection and Analysis

The data collected by the pre-and post-educational questionnaire was transferred into a Microsoft Excel spreadsheet. Confidence was analyzed using SPSS software. The Wilcoxon test was best suited to determine if willingness and awareness to changed anesthetic practices as hypothesized.

Ethical Considerations

Internal Review Board (IRB) approval was obtained prior to initiating this DNP project. Both the project site IRB board and Marian University IRB board approval was obtained. Minimal risk was identified for participation in this study since it does not contain vulnerable or special populations, patient information or involvement, or will pose any threat on mental or physical health of its participants. Data obtained during this project was stored on a password protected computer and was not directly shared. Furthermore, personal identifiers were not used in this project which will protect anonymity. The consent process gave the participant information about the study and what will be required of them before consent is obtained. Participants will be allowed to stop the study at any time.

Data Analysis and Results

The educational opportunity was sent to 25 anesthesia providers with eight responses, making it a 32% completion rate. The amount of anesthesia experience ranged from two years to greater than 20 years with five providers having between 5- and 20-years' experience. 50% of the anesthesia providers responded they performed spinal anesthesia for elective cesarean sections *almost always* while 25% performs *often* and 25% performs *sometimes*. Of these responses, over 62% of providers witness the hemodynamic changes associated with spinal anesthesia *sometimes* while 37% witness them *often*. Furthermore, over 87% of the providers state they must administer vasopressor medications, such as phenylephrine or ephedrine to help correct the hemodynamic effects of spinal anesthesia *often* and *almost always*. Nausea and vomiting are another untoward side effect that is commonly associated with the dramatic drops in blood pressure during spinal anesthesia. The results showed that 100% of these anesthesia providers have witnessed some form of this during their clinical practices.

Fortunately, 75% of the selected anesthesia providers were previously aware of the benefits a 5-HT3 antagonist has to offer before spinal anesthesia while 75% of participants *almost always* give Zofran or another 5-HT3 antagonist before performing them. 62% of responses from the pre-educational questionnaire shows participants are *extremely willing* to include a 5-HT3 antagonist into their anesthetic practices, while 12% state they are *somewhat willing*, 12% state they are *neither willing or unwilling* and 12% state they are *extremely unwilling*. This compares to the post-educational questionnaire responses of 87% are *extremely willing*, and 12% are *extremely unwilling* to adopt a 5-HT3 antagonist into their anesthetic

practices. Utilizing the Wilcoxon test to analyze these results, a significance in the pre-educational and post-education questionnaire, a significant difference was not found ($p>0.05$).

The pre-educational also included a free text answer asking for any concerns to giving Zofran before performing a spinal anesthetic, 7 responses stated *none* while one response considered *based on patient's history*. The post-educational questionnaire all contained the response of *none*.

When comparing the knowledge questions from the pre- and post-educational questionnaire, the question of *Which hemodynamic changes are the most prominent in spinal anesthesia?,* had a 75% correct response rate and 25% incorrect response rate before implementing the educational PowerPoint. The same question was asked after reviewing the PowerPoint and received a 100% correct response rate. Furthermore, the question *Which reflex is commonly activated during spinal anesthesia that may contribute to hypotension and bradycardia?,* and *What is the most common sign and symptom of hypotension during cesarean sections*?, both had an 87% correct response rate on the pre-educational questionnaire and a 100% correct response rate on the post-educational questionnaire. Comparing the means of the two samples, a paired t-test was utilized and was a significant difference was found ($p<0.05$).

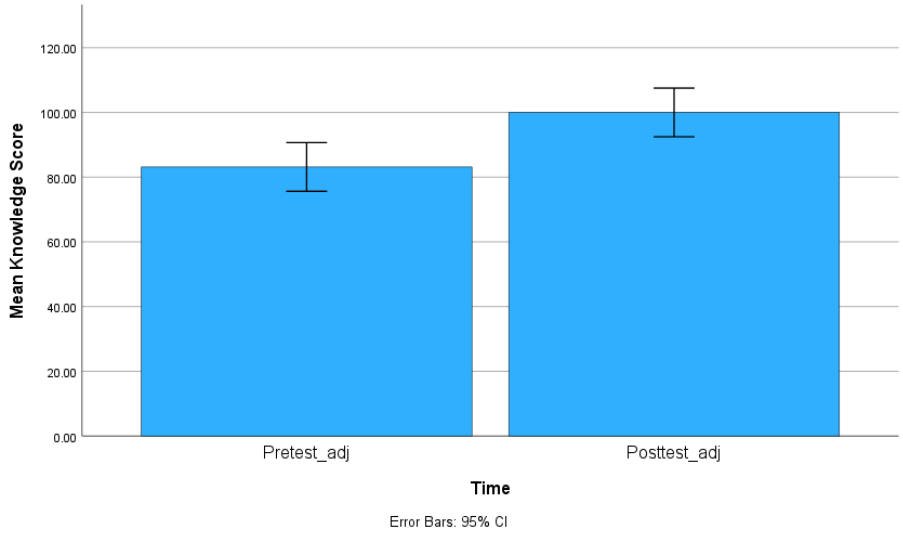


Figure 1: Mean knowledge scores of pre-educational questionnaire and post-educational questionnaire

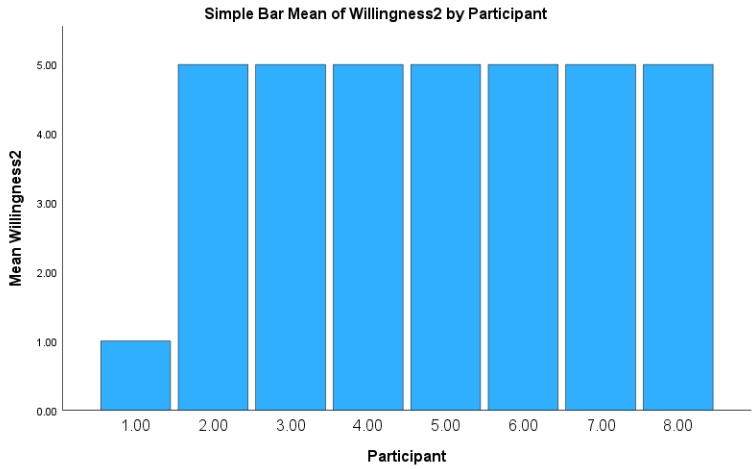


Figure 2: Post-educational questionnaire responses on *willingness*

Discussion

The results shown highlight the impact an educational intervention has on knowledge and learning. When comparing the answers to the pre-educational knowledge questions, the post-educational knowledge questions had significantly improved. Determining the educational intervention was effective by increasing knowledge. However, since most anesthesia providers answered they were already *extremely willing* or *somewhat willing* to adopt a 5-HT3 antagonist into their anesthetic practices before the educational PowerPoint was reviewed, the post-educational results on willingness was not shown to be significant.

The strengths of the study predominantly included easy accessibility. Participants were able to access the questionnaires and educational PowerPoint from anywhere of their choosing. Participation in this study was also done at the participants convenience. The directions to complete the study were organized and listed in numerical fashion to limit any confusion. The information presented was evidence-based research and relevant to the chosen group of participants.

Limitations of this study primarily consisted of the size of the study sample. Although 25 participants were invited to participate in this study, only eight participated. This small of a sample size may not reflect accurately on the overall effectiveness the study had to offer. However, the SPSS tests chosen to represent the data was created to take small sample sizes into account. Another limitation to this study is a sample bias. Although the study was created to include both CRNA's and anesthesiologists, the group of anesthesia providers at the chosen practice site consisted of only CRNA's and were therefore the only anesthesia providers to be included in this project. Lastly, the two-week timeframe to complete the project may have been another limiting factor in the project participation.

Conclusion

Spinal anesthesia, the gold standard of practice for elective cesarean sections commonly produces unpleasant and troublesome side effects, including hypotension and bradycardia. This can trigger detrimental effects on both the mother and baby if left untreated or inappropriately managed. Evidence-based research has recently shown that utilizing a 5-HT3 antagonist such as Zofran, can help to attenuate these effects, decrease vasopressor consumption, and limit the nausea and vomiting caused by hypotension. The implementation of an educational intervention to increase willingness and education of a 5-HT3 antagonist before spinal anesthesia in elective cesarean sections was explored.

Future studies should consider finding a project site that includes both CRNA's and anesthesiologists, as well as either increasing the allotted time to complete the project or consider an in-person intervention in hopes to increase participation. Additionally, exploration of how anesthetic practices have changed since the adoption of this educational intervention may be beneficial.

References

Aksoy, M., Dostbil, A., Aksoy, A., Ince, I., Bedir, Z., & Ozmen, O. (2021). Granisetron or ondansentron to prevent hypotension after spinal anesthesia for elective cesarean delivery: A randomized placebo-controlled trial. *Journal of Clinical Anesthesia*, *75*, 110469. https://doi.org/10.1016/j.jclinane.2021.110469

Alghanem, S., Samarah, W., Bsisu, I., Rahman, Z., Guzu, H., & Abufares, B. (2020). The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between two different doses. *Indian Journal of Anaesthesia*, *64*(11), 954. https://doi.org/10.4103/ija.ija_974_19

Chatterjee, A., Gudiwada, B., Mahanty, P., Kumar, H., Nag, D., Ganguly, P., & Shukla, R. (2020). Effectiveness of granisetron in prevention of hypotension following spinal anaesthesia in patients undergoing elective caesarean section. *Cureus*. https://doi.org/10.7759/cureus.12113

Community Health Network. (2020). *We deliver more than you're expecting*. https://www.ecommunity.com/northbabies

Cusack, L., Del Mar, C. B., Chalmers, I., Gibson, E., & Hoffmann, T. C. (2018). Educational interventions to improve people's understanding of key concepts in assessing the effects of health interventions: A systematic review. *Systematic Reviews*, *7*(1). https://doi.org/10.1186/s13643-018-0719-4

El Khouly, N. I., & Meligy, A. M. (2016). Randomized controlled trial comparing ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during elective

cesarean delivery in egypt. *International Journal of Gynecology & Obstetrics*, *135*(2), 205–209. https://doi.org/10.1016/j.ijgo.2016.06.012

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

Marciniak, A., Owczuk, R., Wujtewicz, M., Preis, K., & Majdyło, K. (2015). The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section: A double-blind, placebo-controlled study. *Polish Gynaecology*, *86*(6), 461–467. https://doi.org/10.17772/gp/2405

Marx, G. (1994). The first spinal anesthesia-Who deserves the laurels? *Regional Anesthesia*, *19*(6), 429–430. https://doi.org/https://oce.ovid.com/article/00002370-199419060-00013/HTML

Nagelhout, J., & Elisha, S. (2018). *Nurse anesthesia* (6th ed.). Elsevier.

Neumann, C., Velten, M., Heik-Guth, C., Strizek, B., Wittmann, M., Hilbert, T., & Klaschik, S. (2020). 5-ht3 blockade does not attenuate postspinal blood pressure change in cesarean section. *Medicine*, *99*(36), e21864. https://doi.org/10.1097/md.0000000000021864

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*, *27*, 25–31. https://doi.org/10.1016/j.ijoa.2016.02.003

Oofuvong, M., Kunapaisal, T., Karnjanawanichkul, O., Dilokrattanaphijit, N., & Leeratiwong, J. (2018). Minimal effective weight-based dosing of ondansetron to reduce hypotension in

cesarean section under spinal anesthesia: A randomized controlled superiority trial. *BMC Anesthesiology*, *18*(1). https://doi.org/10.1186/s12871-018-0568-7

Ortiz-Gómez, J., Palacio-Abizanda, F., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jiménez, A., & Bermejo-Albares, M. (2014). The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: A double-blind, randomised, placebo-controlled trial. *International Journal of Obstetric Anesthesia*, *23*(2), 138–143. https://doi.org/10.1016/j.ijoa.2014.01.005

Ortiz-Gomez, J., Palacio-Abizanda, F., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jiménez, A., & Bermejo-Albares, M. (2017). Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anesthesia: Effect of prophylactic ondansetron and/or continuous infusion of phenylephrine - a double-blind, randomized, placebo controlled trial. *Saudi Journal of Anaesthesia*, *11*(4), 408. https://doi.org/10.4103/sja.sja_237_17

Phipps, L. (2016). *Reducing hypotension in elective cesarean section patients with administration of ondansetron prior to spinal anesthesia: A retrospective chart analysis.* [Doctoral dissertation]. CINAHL.

Qian, J., Liu, L., Zheng, X., & Xiao, F. (2020). Does an earlier or late intravenous injection of ondansetron affect the dose of phenylephrine needed to prevent spinal-anesthesia induced hypotension in cesarean sections? *Drug Design, Development and Therapy*, *Volume 14*, 2789–2795. https://doi.org/10.2147/dddt.s257880

Ranjbar, M., Sheybani, S., & Jahanbin, F. (2018). Prophylactic effects of ephedrine, ondansetron and ringer on hemodynamic changes during cesarean section under spinal anesthesia — a

randomized clinical trial. *Ginekologia Polska*, *89*(8), 454–459. https://doi.org/10.5603/gp.a2018.0078

Šklebar, I. (2019). Spinal anaesthesia-induced hypotension in obstetrics: Prevention and therapy. *Acta Clinica Croatica*. https://doi.org/10.20471/acc.2019.58.s1.13

Stewart, J., Gasanova, I., & Joshi, G. P. (2020). Spinal anesthesia for ambulatory surgery: Current controversies and concerns. *Current Opinion in Anaesthesiology*, *33*(6), 746–752. https://doi.org/10.1097/aco.0000000000000924

Tatikonda, C., Rajappa, G., Rath, P., Abbas, M., Madhapura, V., & Gopal, N. (2019). Effect of intravenous ondansetron on spinal anesthesia-induced hypotension and bradycardia: A randomized controlled double-blinded study. *Anesthesia: Essays and Researches*, *13*(2), 340. https://doi.org/10.4103/aer.aer_22_19

Terkawi, A. S., Tiouririne, M., Mehta, S. H., Hackworth, J. M., Tsang, S., & Durieux, M. E. (2015). Ondansetron does not attenuate hemodynamic changes in patients undergoing elective cesarean delivery using subarachnoid anesthesia. *Regional Anesthesia and Pain Medicine*, *40*(4), 344–348. https://doi.org/10.1097/aap.0000000000000274

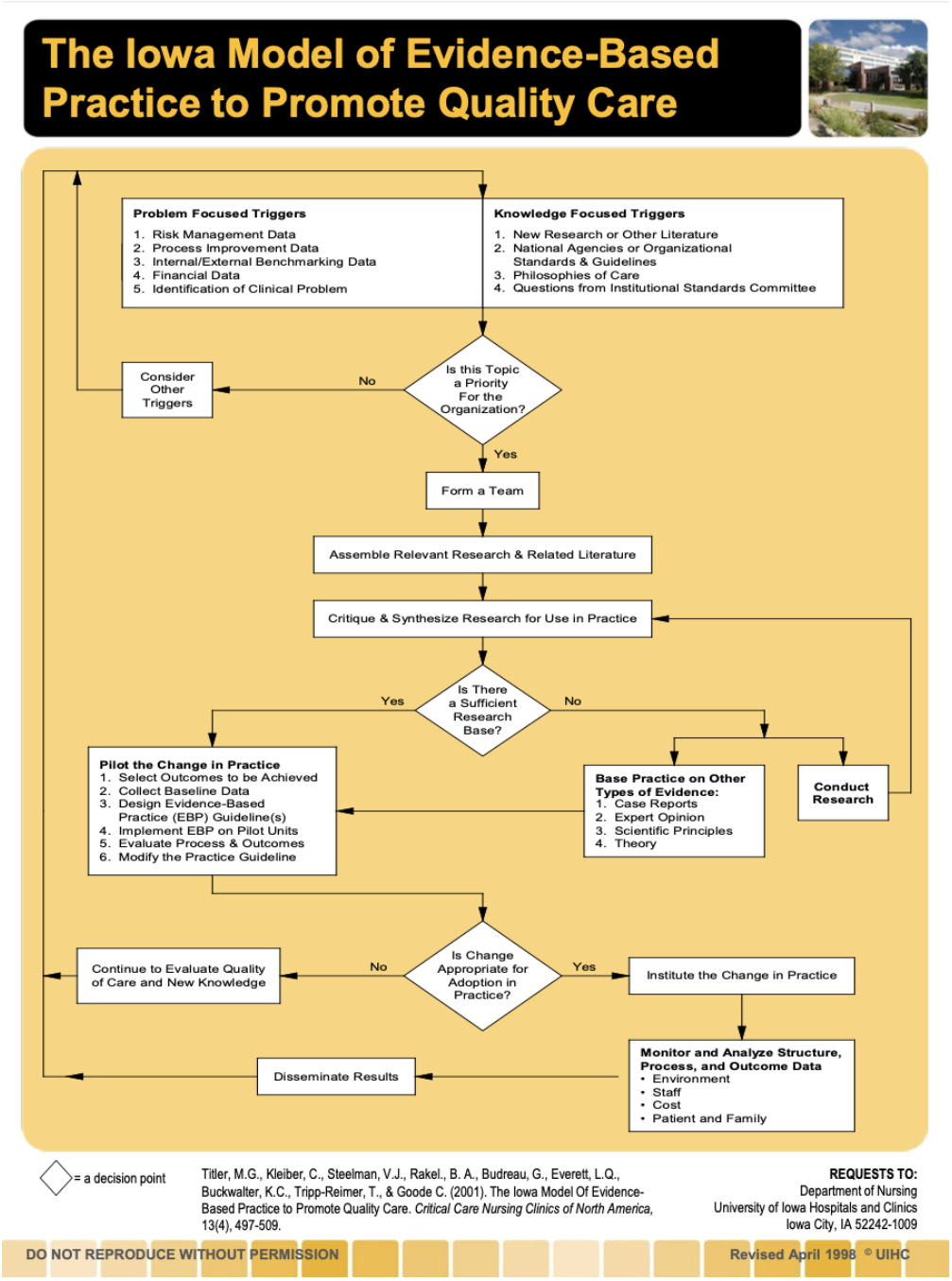
Wang, Q., Zhuo, L., Shen, M.-K., Yu, Y.-Y., Yu, J.-J., & Wang, M. (2014). Ondansetron preloading with crystalloid infusion reduces maternal hypotension during cesarean delivery. *American Journal of Perinatology*, *31*(10), 913–922. https://doi.org/10.1055/s-0033-1364189

Xiao, F., Wei, C., Chang, X., Zhang, Y., Xue, L., Shen, H., Ngan Kee, W. D., & Chen, X. (2019). A prospective, randomized, double-blinded study of the effect of intravenous ondansetron on the effective dose in 50% of subjects of prophylactic phenylephrine infusions for preventing spinal anesthesia–induced hypotension during cesarean delivery.

Anesthesia & Analgesia, *131*(2), 564–569.

https://doi.org/10.1213/ane.0000000000004534

Appendix A: Iowa Model of Evidence-Based Practice to Promote Quality Care



Used/reprinted with permission from the University of Iowa Hospitals and Clinics, copyright 2015. For permission to use or reproduce, please contact the University of Iowa Hospitals and Clinics at 319-384-9098.

Appendix B: Literature Review Matrix

Citation	Research Design & Level of Evidence	Population / Sample size n=x	Major Variables	Instruments / Data collection	Results
Aksoy, M., Dostbil, A., Aksoy, A., Ince, I., Bedir, Z., & Ozmen, O. (2021). Granisetron or ondansentron to prevent hypotension after spinal anesthesia for elective cesarean delivery: A randomized placebo-controlled trial. *Journal of Clinical Anesthesia*, *75*, 110469.	Randomized Controlled Trial, level 2	N=120 40=8mg Zofran 40=3mg granisetron 40=normal saline	Hypotension, vasopressor requirements, nausea and vomiting, APGAR scores	Mean blood pressure, VAS scores, APGAR scores 1 and 5 minutes after birth	Both 3mg of granisetron and 8mg of Ondansetron before spinal anesthesia produced significantly lower ephedrine requirements compared to the placebo.
Chatterjee, A., Gudiwada, B., Mahanty, P., Kumar, H., Nag, D., Ganguly, P., & Shukla, R. (2020). Effectiveness of granisetron in prevention of hypotension following spinal anaesthesia in patients undergoing elective caesarean section. *Cureus*.	Randomized controlled trial, level 2	N=200 100=normal saline 100=1mg granisetron	Vital parameters including systolic, diastolic and MAP, HR, and SpO2, incidence of hypotension, APGAR scores	Fall in the systolic arterial blood pressure below 100mmHg or a fall in mean arterial blood pressure of more than 20% from baseline value was taken as hypotension, vital signs, APGAR	Normal saline group had 69% hypotension while granisetron group had 37% and NS group required more mephentermine. APGAR scores were comparable between the two groups.
Alghanem, S., Samarah, W., Bsisu, I., Rahman, Z., Guzu, H., & Abufares, B. (2020). The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between	Randomized controlled trial, level 2	N=152 51=4mg Zofran 51=8mg Zofran 50=Normal Saline	Systolic blood pressure, diastolic blood pressure, MAP	Systolic, diastolic, MAP	No significant difference among blood pressure changes in all groups, however, ephedrine requirements is higher in the normal saline group.

two different doses. *Indian Journal of Anaesthesia*, *64*(11), 954.					
Neumann, C., Velten, M., Heik-Guth, C., Strizek, B., Wittmann, M., Hilbert, T., & Klaschik, S. (2020). 5-ht3 blockade does not attenuate postspinal blood pressure change in cesarean section. *Medicine*, *99*(36), e21864	Retrospective chart study, level 3	N=160 80=8mg Zofran 80=normal saline	Blood pressure, heart rate, vasopressor use, fluid intake, maternal and infantile outcomes	Vital signs, vasopressor administration, crystalloid fluid, APGAR, cord blood pH, base excess	8 mg Zofran does not effectively attenuate post spinal change in maternal blood pressure during cesarean section
Xiao, F., Wei, C., Chang, X., Zhang, Y., Xue, L., Shen, H., Ngan Kee, W. D., & Chen, X. (2019). A prospective, randomized, double-blinded study of the effect of intravenous ondansetron on the effective dose in 50% of subjects of prophylactic phenylephrine infusions for preventing spinal anesthesia–induced hypotension during cesarean delivery. *Anesthesia & Analgesia*, *131*(2), 564–569.	Randomized controlled trial, level 2	N=60 30=Normal saline 30=4mg Zofran	Phenylephrine infusion rate, hypotension, hypertension, heart rate, fetal outcomes, N&V, shivering	ED50 of phenylephrine infusion, vital signs, APGAR scores, arterial umbilical blood pH	Intravenous ondansetron 4 mg reduced the ED50 of a prophylactic phenylephrine infusion by approximately 26% in patients undergoing cesarean delivery under combined spinal-epidural anesthesia.
Qian, J., Liu, L., Zheng, X., & Xiao, F. (2020). Does an earlier or late intravenous injection of ondansetron affect the dose of phenylephrine needed to prevent spinal-anesthesia induced hypotension in cesarean sections? *Drug Design, Development and Therapy*, *Volume 14*, 2789–2795	Randomized controlled trial, level 2	N=75 25=Ondansetron given 5 min before spinal 25=Ondansetron given 15 min before spinal 25=Normal saline	Blood pressure, heart rate, phenylephrine infusion rates	Systolic, diastolic, MAP, heart rate, phenylephrine infusion	Earlier administration of 4 mg prophylactic ondansetron contributed no benefits for lowing the dose of prophylactic phenylephrine compared to a late administration but can decrease the dose of preventing phenylephrine in patients undergoing cesarean sections.

Tatikonda, C., Rajappa, G., Rath, P., Abbas, M., Madhapura, V., & Gopal, N. (2019). Effect of intravenous ondansetron on spinal anesthesia-induced hypotension and bradycardia: A randomized controlled double-blinded study. *Anesthesia: Essays and Researches*, *13*(2), 340.	Randomized controlled trial, level 2	N=140 70=4mg ondansetron 70=Normal saline	Blood pressure, heart rate, shivering	Systolic, diastolic, MAP, shivering, ephedrine requirements, atropine requirements	Prophylactic use of ondansetron before spinal anesthesia significantly reduces the requirement of ephedrine and shivering
Ortiz-Gomez, J., Palacio-Abizanda, F., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jiménez, A., & Bermejo-Albares, M. (2017). Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anesthesia: Effect of prophylactic ondansetron and/or continuous infusion of phenylephrine - a double-blind, randomized, placebo controlled trial. *Saudi Journal of Anaesthesia*, *11*(4), 408.	Randomized controlled trial, level 2	N=265 4 random groups not specified. Normal saline, 8 ondansetron , phenylephrine infusion, 8mg ondansetron and phenylephrine	Blood pressure, heart rate, adverse events, vasopressor requirements, atropine	Vital signs, presence of N&V and pruritis, atropine requirements, ephedrine requirements, phenylephrine requirements.	A 50 μg/min phenylephrine infusion reduces by 50% the incidence of maternal hypotension compared with placebo. Prophylactic ondansetron 8 mg does not reduce the incidence of maternal hypotension but diminishes its severity, reducing the number of hypotensive events per patient by 50%.
Oofuvong, M., Kunapaisal, T., Karnjanawanichkul, O., Dilokrattanaphijit, N., & Leeratiwong, J. (2018). Minimal effective weight-based dosing of ondansetron to reduce hypotension in cesarean section under spinal anesthesia: A randomized controlled superiority trial. *BMC Anesthesiology*, *18*(1).	Randomized controlled trial, level 2	N=215 72=normal saline 71=Zofran 0.05mg/kg 72=0.1mg/kg Zofran	Vital signs, vasopressor use, adverse events	Blood pressure, heart rate, ephedrine requirements, metoclopramide requirements	Ondansetron 0.05 mg/kg or 0.1 mg/kg administered before spinal anesthesia did not reduce the incidence of hypotension. Metoclopramide requirements were lower in 0.1mg/kg group compared to control.

Karacaer, F., Biricik, E., Ünal, İ., Büyükkurt, S., & Ünlügenç, H. (2017). Does prophylactic ondansetron reduce norepinephrine consumption in patients undergoing cesarean section with spinal anesthesia? *Journal of Anesthesia*, *32*(1), 90–97.	Randomized controlled trial, level 2	N=108 54=8mg ondansetron 54=normal saline	Hypotensive episodes, adverse events, norepinephrine consumption	Systolic, diastolic, MAP, heart rate, spO2, episodes of hypotension, norepinephrine consumption, nausea & vomiting, episodes of bradycardia	8mg Zofran 5 minutes before spinal anesthesia did not prevent spinal-induced hypotension, however, cumulative episodes of hypotension and norepinephrine consumption were significantly greater in normal saline group (p=0.009).
Ranjbar, M., Sheybani, S., & Jahanbin, F. (2018). Prophylactic effects of ephedrine, ondansetron and ringer on hemodynamic changes during cesarean section under spinal anesthesia — a randomized clinical trial. *Ginekologia Polska*, *89*(8), 454–459.	Randomized controlled trial, level 2	N=90 30=4mg ondansetron 30=lactated ringer 30=25mg IM Ephedrine	Hypotension, bradycardia, N&V, shivering	Systolic, diastolic, MAP, heart rate, incidence of bradycardia and hypotension, nausea and vomiting, shivering.	IM Ephedrine 25 minutes prior to spinal anesthesia led to best prevention of systolic blood pressure changes
El Khouly, N. I., & Meligy, A. M. (2016). Randomized controlled trial comparing ondansetron and placebo for the reduction of spinal anesthesia-induced hypotension during elective cesarean delivery in egypt. *International Journal of Gynecology & Obstetrics*, *135*(2), 205–209.	Randomized controlled trial, level 2	N=100 50=4mg ondansetron 50=normal saline	Hypotension, bradycardia, adverse events	Systolic, diastolic, MAP, N&V, Heart rate, ephedrine use, atropine use, shivering	IV ondansetron significantly reduced hypotension and fluctuations in heart rate. Nausea and vomiting were also reduced.
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*	Randomized controlled trial, level 2	N=168 56=10mg IV Ephedrine 56=8mg ondansetron 56=normal saline	Blood pressure, N&V, APGAR, intraoperative vasopressor use	Systolic, diastolic, MAP, incidence of N&V, vasopressor use, APGAR scores,	No significant difference in maternal blood pressure, however, 8mg ondansetron group required less norepinephrine use than normal saline group.

of Obstetric Anesthesia, *27*, 25–31.					
Marciniak, A., Owczuk, R., Wujtewicz, M., Preis, K., & Majdyło, K. (2015). The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section: A double-blind, placebo-controlled study. *Polish Gynaecology*, *86*(6), 461–467.	Randomized controlled trial, level 2	N=72 35=8mg ondansetron 34=normal saline	Blood pressure, heart rate	Systolic, diastolic, heart rate	There was not a significant reduction in blood pressure changes.
Wang, Q., Zhuo, L., Shen, M.-K., Yu, Y.-Y., Yu, J.-J., & Wang, M. (2014). Ondansetron preloading with crystalloid infusion reduces maternal hypotension during cesarean delivery. *American Journal of Perinatology*, *31*(10), 913–922.	Randomized controlled trial, level 2	N=66 33=4mg ondansetron 33=normal saline	Blood pressure, heart rate, umbilical cord blood samples	Systolic, MA, episodes of hypotension, incidence of nausea, umbilical venous pH, phenylephrine use	Ondansetron preloading combined with crystalloid infusion significantly reduced hypotension and nausea, improved acid-base status, and reduced vasopressor use.
Terkawi, A. S., Tiouririne, M., Mehta, S. H., Hackworth, J. M., Tsang, S., & Durieux, M. E. (2015). Ondansetron does not attenuate hemodynamic changes in patients undergoing elective cesarean delivery using subarachnoid anesthesia. *Regional Anesthesia and Pain Medicine*, *40*(4), 344–348.	Randomized controlled trial, level 2	N=86 44=8mg ondansetron 42=placebo	Vital signs, N&V, pruritis, vasopressors.	Systolic, diastolic, MAP, heart rate, episodes of nausea and vomiting, episodes of pruritis, phenylephrine use	Ondansetron does not reduced hemodynamic changes before spinal anesthesia nor does it reduce incidence of nausea and vomiting, pruritis, or vasopressor consumption.
Phipps, L. (2016). *Reducing hypotension in elective cesarean section patients with administration of*	Retrospective study, level 3	N=114	Blood pressure, vasopressors.	Systolic, diastolic, MAP, vasopressor use	No significant difference with ondansetron administration, however, decreased use of vasopressor use to maintain blood pressure.

ondansetron prior to spinal anesthesia: A retrospective chart analysis. [Doctoral dissertation]. CINAHL.					

Appendix C: Pre-Educational Questionnaire

1. How long have you been an anesthesia provider?
    a. <1 year
    b. 1-5 years
    c. 5-20 years
    d. >20 years

2. How often do you perform spinal anesthesia for elective cesarean sections?
    a. Never
    b. Sometimes
    c. Often
    d. Almost always

3. How often do you give a 5-HT3 antagonist, such as Zofran, before your spinal anesthetic in cesarean sections?
    a. Never
    b. Sometimes
    c. Often
    d. Almost always

4. How often do you witness hemodynamic changes associated with spinal anesthesia in cesarean sections?
    a. Never
    b. Sometimes
    c. Often
    d. Always

5. Which hemodynamic changes are the most prominent in spinal anesthesia? Select TWO
    a. Hypertension
    b. Increased SNS tone
    c. Hypotension
    d. Bradycardia
    e. Tachycardia

6. Which reflex is commonly activated during spinal anesthesia that may contribute to hypotension and bradycardia?
    a. Bainbridge reflex
    b. Celiac reflex
    c. Baroreceptor reflex
    d. Bezold-Jarisch reflex
    e. Vagal response

7. What is the most common sign and symptom of hypotension during cesarean sections?
    a. Irritability
    b. Pain
    c. Unconsciousness
    d. Nausea and vomiting

8. How often do you give a vasopressor, such as phenylephrine or ephedrine, after performing spinal anesthesia in a cesarean section?
    a. Never
    b. Sometimes
    c. Often
    d. Always

9. How often do you witness nausea and vomiting associated with spinal-induced hypotension?
    a. Never
    b. Sometimes
    c. Often
    d. Always

10. Are you aware of the benefits a 5-HT3 antagonist, such as Zofran, may offer before performing a spinal anesthetic in cesarean sections?
    a. Yes
    b. No

11. How willing are you to include a 5-HT3 antagonist, such as Zofran, as part of your anesthetic before spinal anesthesia in cesarean sections? (1) Extremely unwilling (2) Somewhat unwilling (3) Neither willing or unwilling (4) Somewhat willing (5) Extremely willing.
    a. 1
    b. 2
    c. 3
    d. 4
    e. 5

12. What is a hesitation, if any, of giving Zofran prior to performing a spinal?

Appendix D: Post-Educational Questionnaire

1. Which hemodynamic changes are the most prominent in spinal anesthesia? Select TWO
    a. Hypertension
    b. Increased SNS tone
    c. Hypotension
    d. Bradycardia
    e. Tachycardia

2. Which reflex is commonly activated during spinal anesthesia that may contribute to hypotension and bradycardia?
    a. Bainbridge reflex
    b. Celiac reflex
    c. Baroreceptor reflex
    d. Bezold-Jarisch reflex
    e. Vagal response

3. What is the most common sign and symptom of hypotension during cesarean sections?
    a. Irritability
    b. Pain
    c. Unconsciousness
    d. Nausea and vomiting

4. Are you aware of the benefits a 5-HT3 antagonist, such as Zofran, may offer before performing a spinal anesthetic in cesarean sections?
    a. Yes
    b. No

5. How willing are you to include a 5-HT3 antagonist, such as Zofran, as part of your anesthetic before spinal anesthesia in cesarean sections? (1) Extremely unwilling (2) Somewhat unwilling (3) Neither willing or unwilling (4) Somewhat willing (5) Extremely willing.
    a. 1
    b. 2
    c. 3
    d. 4
    e. 5

6. What is a hesitation, if any, of giving Zofran prior to performing a spinal?

Appendix E: Community Health Network IRB Approval Letter

Community Health Network

Institutional Review Board
7330 Shadeland Station
Indianapolis, IN 46256
O 317.355.5675
F 317.957.3939
IRB@eCommunity.com

December 21, 2022

RE: NOTIFICATION OF EXPEDITED APPROVAL – NEW PROTOCOL

PI: Jimison, Madison J, DNP
IRB # 2022-482
Study #: Zofran Education
Reference # 004204
TITLE: Ondansetron before spinal anesthesia in cesarean sections: An evidence-based educational intervention

The Community Health Network Institutional Review Board (IRB) has reviewed the above-referenced protocol. In compliance with Federal Regulations [21 CFR 56.109(e); 45 CFR 46.109(d)] this letter serves as your written notification of the IRB's determination.

The Protocol meets the criteria for Expedited Review per 21 CFR 56.110 and/or 45 CFR 46.110 and **is approved under Expedited Category 7 as set forth in 63 FR 60364-60367:**

The approval is valid from 12/21/2022 to 12/20/2023.

The documents included in this approval are:

• Submission Components		
Form Name	Version	Outcome
Pre-Review Correction Form - IRB	Version 2.0	Approved
Pre-Review Correction Form - IRB	Version 1.0	Approved
Initial Review Submission Packet	Version 1.0	Approved
Study Application - IRB	Version 1.1	Approved

Study Document			
Title	Version #	Version Date	Outcome
Protocol	Version 1.1	12/07/2022	Approved
Ondansetron before Spinal Anesthesia in Cesarean Sections	Version 1.0	11/28/2022	Approved
NNRC approval jimison 2022	Version 1.0	09/29/2022	Approved
posteducational questionnaire	Version 1.0	11/28/2022	Approved
preeducational Questionnaire	Version 1.0	11/28/2022	Approved

Study Consent Form			
Title	Version #	Version Date	Outcome
Informed Consent for Voluntary Project Participation	Version 1.0	11/28/2022	Approved

Approval of this protocol is based on your agreement to abide by the policies and procedures of the Community Health Network regarding research and to keep appropriate records concerning your subjects. Any serious reactions resulting from this study should be reported immediately to the IRB and study sponsor (if applicable).

IRB approval is required prior to implementing any changes or amendments to the protocol, regardless of how minor, except to eliminate apparent hazards to study subjects. No changes to the Informed Consent Document may be made without prior IRB review and approval.

The approval period is noted above. Please be advised that continued approval is contingent upon submission of a renewal application **no later than thirty days before 12/20/2023.** Failure to submit the renewal notice in a timely fashion may result in the expiration and subsequent administrative withdrawal of the protocol.

Failure to receive notification from the IRB Office will not alleviate your responsibility to ensure compliance with Federal Regulations regarding annual renewal [21 CFR 56.109(f); 45 CFR 46.109(e)]. Should you fail to obtain re-approval of the above-named study prior to the expiration date, all research activity must cease until re-approval is established. Regulations make no provisions for a grace period regarding the continuation of research beyond the expiration date.

The continuation of research after expiration of IRB approval is a violation of Federal Regulations [21 CFR 56.103(a)] and Community Health Network policy.

Please refer to the IRB-assigned number and exact study title in future correspondence with the IRB Office. You should retain a copy of this letter and all associated study documents for your records. All documentation related to this study must be maintained in your files for audit purposes for at least three (3) years after the closure of the research.

If you have any questions or require assistance in preparing your response, please contact the IRB Office at (317) 355-5675 or via email at IRB@eCommunity.com .

Sincerely,

Randall A. Lee MD

Signature applied by Randy Lee on 12/21/2022 03:37:57 PM EST

Appendix F: Marian University IRB Approval Letter

MARIAN UNIVERSITY
Indianapolis ®

Institutional Review Board

DATE:	1-12-2023
TO:	Madison Jimison & Dr. Derrianne Monteiro
FROM:	Institutional Review Board
RE:	S23.107
TITLE:	Ondansetron Before Spinal Anesthesia in Cesarean Sections: An Evidenced-Based Educational Intervention
SUBMISSION TYPE:	New Project
ACTION:	Determination of EXEMPT Status
DECISION DATE:	1-12-2023

The Institutional Review Board at Marian University has reviewed your protocol and has determined the procedures proposed are appropriate for exemption under the federal regulations. As such, there will be no further review of your protocol and you are cleared to proceed with your project. The protocol will remain on file with the Marian University IRB as a matter of record.

Although researchers for exempt studies are not required to complete online CITI training for research involving human subjects, the IRB **recommends** that they do so, particularly as a learning exercise in the case of student researchers. Information on CITI training can be found on the IRB's website: http://www.marian.edu/academics/institutional-review-board.

It is the responsibility of the PI (and, if applicable, the faculty supervisor) to inform the IRB if the procedures presented in this protocol are to be modified of if problems related to human research participants arise in connection with this project. Any procedural modifications must be evaluated by the IRB before being implemented, as some modifications may change the review status of this project. Please contact me if you are unsure whether your proposed modification requires review. Proposed modifications should be addressed in writing to the IRB. **Please reference the above IRB protocol number in any communication to the IRB regarding this project.**

Amanda C. Egan, Ph.D.
Chair, Marian University Institutional Review Board