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Does Administration Timing of Ondansetron, a 5-HT3 Receptor Antagonist, Affect Inhibition of the Bezold-Jarisch Reflex in OB C-section Patients Receiving Spinal Anesthesia

Spenser Zaharie
University of Pennsylvania, zaharie@nursing.upenn.edu

Matthew Rowley
University of Pennsylvania, mprowley@nursing.upenn.edu

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Abstract

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Keywords

ondansetron, bezold-jarisch reflex, spinal anesthesia, cesarean section

Disciplines

Nursing

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Matthew P Rowley and Spenser C Zaharie

University of Pennsylvania

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Abstract

Ondansetron (a 5HT-3 receptor antagonist) has been shown in multiple randomized controlled trials (RCT's) and meta-analysis to inhibit activation of Bezold-Jarisch Reflex (BJR) in response to spinal anesthesia for elective cesarean section patients. Studies have not determined whether the timing of administration changes the inhibitory affect of ondansetron in this patient population. This project addressed the following question: Does administration timing of Ondansetron, a 5-HT3 receptor antagonist, affect inhibition of the Bezold-Jarisch Reflex in obstetric cesarean section patients receiving spinal anesthesia? De-identified aggregated electronic medical record data for a one-year period was obtained. Data was grouped by ondansetron administration timing prior to spinal administration: ≤ 15 minutes (G1), > 15 minutes and ≤ 30 minutes (G2), > 30 minutes (G3). Blood Pressure (BP) data, including systolic, diastolic and mean arterial pressure (MAP), was included for four time points: pre spinal, 5-, 15- and 30-minutes post spinal. Change in BP from baseline were used for analysis. Total vasopressor usage was also included for analysis. Sixty-six obstetric cases were included, (G1 n=24), (G2 n=24) and (G3 n=18). Data was analyzed using the one-way ANOVA test for BP change scores and the Kruskal-Wallis for evaluating vasopressor use. No statistical significance between groups was found in BP change scores or vasopressor use. However, G3 did show greater drops in BP and increased vasopressor usage compared to G2 and G1. Further evaluation is recommended through either a large-scale retrospective study or randomized control trial (RCT).

Keywords: *Ondansetron, Bezold-Jarisch Reflex, Spinal Anesthesia, Cesarean Section.*

Does Ondansetron as a 5-HT3 Receptor Antagonist Inhibit the Bezold-Jarisch Reflex in OB C-section Patients Receiving Spinal Anesthesia

Hypotension and bradycardia are two of the most common side effects of spinal anesthesia prior to cesarean section. This is due to multiple events related to the anesthetics sympathetic blockade resulting, in part, due to activation of the Bezold-Jarisch Reflex. Current practice dictates the use of preloading with crystalloid solution and treating hypotension/bradycardia with vasoactive medication. Current research suggests that the use of ondansetron, a 5HT-3 receptor antagonist, can be utilized to block this reflex pathway.

Background and Significance

Spinal anesthesia has been the gold standard of anesthetic administration for cesarean section patients. Sensory blockade of T4 is needed to cover the surgical area involved in this procedure. Due to this level of blockade, two of the most frequent side effects can be profound hypotension and bradycardia.

After administration of the spinal anesthetic, the parturient patient undergoes loss of sympathetic stimulation. The effect is a drop in systemic vascular resistance (SVR) along with decreased venous return due to the resulting peripheral vasodilation. Reduction in venous return results in increased cardiac hypercontraction due to decreased afterload. Mechanoreceptors in the left ventricle are activated, which in turn causes bradycardia and hypotension due to increased parasympathetic stimulation. This response is known as the Bezold-Jarisch reflex (BJR) (Nagelhout & Elisha, 2018).

Maternal hypotension as a result of BJR activation can advance into certain life threatening conditions for the baby as well as the mother. Untreated spinal induced hypotension can lead to worsening hemodynamic instability, and potential cardiovascular collapse (Miller and

Pardo, 2018). This can also lead to greater drops in fetal pH, as well as increased fetal base deficits (Reynolds & Seed, 2005).

There are several approaches anesthetists utilize to treat these side effects. These approaches include preloading/co-loading with crystalloid solution, administering intravenous (IV) vasoactive medications, and placing the patient in the left lateral or Trendelenburg position. Each of these approaches have been shown to mitigate these side effects (Chestnut et al., 2020).

Problem Statement

Without prophylactic management, about 80% of parturient patients receiving this type of anesthesia will present with maternal hypotension (Ryu et al., 2019). Sustained hypotension can lead to decreased uteroplacental perfusion which can lead to fetal hypoxia, acidosis, and neonatal depression. Adverse maternal outcomes can include altered levels of consciousness, aspiration, apnea, and cardiac arrest (Chestnut et al., 2020). Studies on the effects of vasopressors in this setting are inconsistent in efficacy results (Ryu et al., 2019). Research on preload/co-load crystalloid fluid administration has been shown to be minimally effective(Chestnut et al., 2020). Currently there is no single intervention that “prevents” spinal induced hypotension for patients undergoing cesarean section.

Recent studies have looked into preventing spinal induced hypotension by blocking the BJR at the nerve receptor sites. Warltier et al. (2003) suggest the BJR is caused by activation of 5-HT3 serotonin receptors located on unmyelinated c-fibers originating in the cardiac muscle. Yamano et al. (1995) also demonstrated through animal studies that selective 5-HT3 receptor antagonists can help inhibit the BJR when serotonin is injected directly into the bloodstream of rats. Through the blockade of the 5-HT3 receptor, parasympathetic response may be attenuated to prevent hypotension. Ondansetron, a 5-HT3 antagonist routinely used for post-operative

nausea and vomiting, can potentially be used to help block this reflex depending on the timing of administration. Does administration timing of ondansetron, a 5-HT3 receptor antagonist, affect inhibition of the BJR in OB c-section patients receiving spinal anesthesia?

Literature Review

Methods

Databases used for literature search included “PubMed” and “Franklin Database”. Search phrase consisted of “Ondansetron and spinal anesthesia and hypotension” for each database. The “and” in both database searches were Boolean operators.

The PubMed search resulted in 38 articles found. Search was narrowed to within the last 8 years (2012-2020). Thirteen publications were excluded due to being unrelated to administration of ondansetron pre-spinal anesthesia. Twenty-five publications were retained for further review based on inclusion criteria of drug used (ondansetron), administration prior to spinal anesthesia, and hypotension. See Figure 1 for PRISMA diagram.

The Franklin Database search was narrowed to peer reviewed publications only, and publications within the last 10 years (2010-2020). One hundred results were found using this method. Database delimiter words consisted of analgesia, analgesics, analgesic opioid administration and dosage, analgesic opioid adverse effects, analgesics opioid therapeutic use, clonidine, dexamethasone, dexmedetomidine, fentanyl, ketamine, laparoscopic surgery, laparoscopy, male, morphine, narcotics, nausea, opioids, pain, pain management, pain measurement, pain medicine, pain postoperative, pain postoperative drug therapy, pain postoperative prevention and control, patient satisfaction, postoperative analgesia, postoperative nausea, postoperative nausea and vomiting prevention and control, postoperative pain, postoperative period, propofol, ropivacaine, shivering, and vomiting. The PubMed database was

then excluded in the Franklin search criteria due to already being searched as stated above. Fifty-seven publications were found according to the new criteria. Publications were screened and 53 were excluded for relevancy due to being unrelated to administration of ondansetron pre-spinal anesthesia. Six of the publications were retained for review based on inclusion criteria of drug used (ondansetron), administration prior to spinal anesthesia, and hypotension.

Four publication duplicates were found and removed between the two database results. This resulted in 27 full-text articles assessed for full eligibility criteria. Publications were then excluded due to the type of drug used (not ondansetron 5HT-3 receptor antagonists), surgery performed (not cesarean section), crystalloid co-administration, vasopressor co-administration, study sample size less than 50, weight-based dosing of ondansetron, and date of publication prior to 2014. Ten publications were included in this review.

Data Evaluation

The Consort 2010 checklist (Moher, 2010) was utilized for evaluating the quality of the randomized controlled trials (RCT's). The Center of Evidence Based Medicine (CEBM) checklist (University of Oxford, 2020) was utilized for evaluating the meta-analysis and systematic reviews. The Johns Hopkins Evidence Level and Quality Guide (Dang & Dearholt, 2018) was also utilized for grading the quality of all studies evaluated.

Consort 2010 provides a checklist of RCT-specific elements that should be included in all trials. The checklist contains 25 items that appraise the title and abstract, introduction, methods, results, discussion, as well as other information related to the study. Upon appraisal using this checklist, the studies were then assigned a level of evidence (1-5), and a quality of evidence (A, B, or C) using the Johns Hopkins Evidence Level and Quality Guide (Dang & Dearholt, 2018).

The CEBM (University of Oxford, 2020) was used to evaluate the meta-analysis and systematic reviews. This tool asks a series of six questions evaluating the question presented, the relevancy of the study, inclusion/exclusion criteria, the validity of the included studies and the similarity of results from study-to-study. The studies were then assigned a level of evidence (1-5), and a quality of evidence (A, B, or C) using the Johns Hopkins Evidence Level and Quality Guide (Dang & Dearholt, 2018).

Results

Ten studies were included in the review and evaluated. All studies investigated the administration of ondansetron at five minutes prior to spinal administration. Six of the studies were RCTs and four were meta-analyses (See Table 1).

Mareshi et al. (2014) found that administering 6mg and 12mg of IV ondansetron significantly attenuated spinal induced hypotension. They also found an increased requirement of vasopressors in the control group compared to the experimental group ($p=0.04$). Shabana et al. (2018) administered 4 mg of ondansetron IV to an experimental group, and found drops in arterial blood pressures were significantly reduced ($p=0.007$) and required less vasopressor medication compared to the control group ($p=0.005$). Trabelsi et al. (2015) concluded patients who received ondansetron in the experimental group prior to spinal administration experienced decreased amounts of hypotension ($p<0.001$) compared to the control group. Vasopressor usage was also significantly decreased ($p\leq0.001$) in the experimental group. Wang et al. (2014) evaluated different dosing of ondansetron in experimental groups. The findings suggested patients who received 4 or 6mg ondansetron experienced significantly reduced incidences ($p\leq0.05$) of hypotension. Those that received 2 or 8mg ondansetron were observed to experience only minimal decreases ($p\geq0.05$) in hypotension compared to the control group.

Tatikonda, et al. (2019) and Ortiz, et al. (2014) found non-significant results regarding ondansetron affect on hypotension. Ortiz, et al. (2014) found no significant difference for hypotension between the placebo and ondansetron groups (p=0.77). The authors attributed their results to the use of fentanyl in the spinal administration which may have led to more pronounced hypotension. This study excluded any patient with a BMI over 30 kg/m^2, which may have limited the study to a specific population different from other studies included in the review. Further, the results may be less representative of the general c-section population. However, this study did show that the need for vasopressor use was decreased after administration of ondansetron, which does illustrate a benefit of ondansetron usage. Tatikonda, et al. (2019) demonstrated similar results in that blood pressure was not significantly affected ($p > 0.05$) by ondansetron, but vasopressor usage was lower in the experimental group compared to the control group (p=0.029).

Three meta-analyses examined in the literature showed that the prophylactic use of ondansetron can help alleviate spinal anesthesia induced hypotension. Tubog, et al. (2017) evaluated nine RCT's (N= 984) specifically involving parturient patients receiving spinal anesthesia for cesarean section. Five of the RCTs showed decreased hypotension and pooled data results showed ondansetron did attenuate hypotension in the parturient patient groups (RR 0.63; CI, 0.45-0.88). Gao, et al. (2015) included six obstetric RCTs (N=452) where ondansetron was given prior to spinal administration. Gao, et al. (2015) findings suggest that ondansetron reduced hypotension (RR=0.47; 95% CI 0.35-0.63) caused by spinal anesthesia administration as well as decreased ephedrine use (-2.35mg; 95% CI –4.14, –0.55mg) and phenylephrine (-31.16 mcg; 95% CI -57.46, –4.87 mcg). Heesen et al. (2016) evaluated seven RCTs of obstetric patients

(N=706). Findings suggested that ondansetron was effective (RR 0.70; 95% CI 0.49-0.99) in reducing hypotension in parturient cesarean section patients.

Zhou et al. (2018) evaluated 21 RCTs of parturient patients undergoing cesarean section. Only five of these RCTs evaluated hypotension specifically (N=362). Their analysis did not show a significant difference in hypotensive response (RR=0.72; 95% CI 0.50, 1.06) during spinal anesthesia. While this study pooled more RCTs compared to the other three meta-analyses, it also had the smallest sample size in regard to hypotension. The study included with the highest risk ratio presented was also dated from 1999 and the aim of the study was not evaluating ondansetron dosing prior to spinal administration. Instead, ondansetron was given intra-op and post spinal anesthesia induction.

Across the included studies, there was consistency in results for the significant reduction of hypotension with ondansetron administration prior to spinal anesthesia in c-section patients. This was similarly affirmed in the included meta-analyses. The strength and quality of evidence is highly supportive of the positive effects of ondansetron for reducing or limiting the untoward side effects of spinal anesthesia in c-section patients. There remains a gap in available trials regarding the timing of ondansetron administration relative to spinal anesthesia.

Organizational Assessment

Protocol at the project site, a large medical center in a suburban area, dictates that 4 mg ondansetron is administered prior to all elective cesarean sections receiving spinal anesthesia for patients with no contraindications. Timing of administration is not standardized at the site. Administration timing varies from 5 minutes to an hour prior to the procedure start. Whether this alters the positive effects of ondansetron on the hypotensive response from spinal anesthesia is not well known.

The project stakeholders included the IT department for data abstraction, CRNA site lead, DNP faculty lead, and site nurse educators. Other stakeholders included the anesthesia providers and hospital administration in providing safe quality care, founded on evidence-based practice.

Project Purpose

This retrospective study explored the effects of ondansetron administration timing on spinal anesthesia hypotension in cesarean section patients at the site. While the use of ondansetron in the prevention of spinal induced hypotension has been studied and is efficacious with pre-spinal administration at 5 minutes, the site's standard of practice for administering ondansetron does not define timing of administration. The goal was to determine through a retrospective analysis of existing data if ondansetron administration timing affects hypotension and the amount of vasopressor usage in this patient population. These results will inform a standardization of practice in accordance with ondansetron delivery timing at the site.

Conceptual and Theoretical Framework

Conceptual Framework

For this project, the Stetler Model was chosen for the conceptual framework. The Stetler Model is used to judge "appropriateness, desirability, feasibility, and manner of using research findings" according to Stetler (2001). This model involves steps that include the evaluation of research to help determine evidence-informed practice. These steps are broken down into five different phases for the development and revision of standards of nursing practice.

Stetler's first phase is considered the preparatory phase. In this phase the project purpose and outcomes are defined. Affirmation of priority, consideration of influential factors, and review of current literature is also taken into consideration (Stetler, 2001). This project is focused

on determining if the delivery of ondansetron reduces spinal induced hypotension in patients receiving spinal anesthesia in elective cesarean sections. This is a priority because hypotension is a common side effect of spinal anesthesia and is associated with poor maternal and fetal outcomes (Chestnut et al., 2020). Research literature regarding ondansetron use to prevent maternal hypotension due to spinal anesthesia for elective cesarean section patients was reviewed and synthesized for the project.

Stetler's second phase of validation includes the critique and synopsis of the literature and determining whether the evidence is subject to rejection. The literature review on this subject was conducted and the findings support this practice (Table 1). The overall level and quality of the evidence of the studies evaluated ranged from 1A to 1C using the Johns Hopkins Evidence Level and Quality Guide (Stetler, 2001).

Phase three is defined as comparative evaluation and decision making. During this phase, four major items are assessed before a decision is made to move forward with the project. The fitness of the setting, the feasibility, current practice, and substantiating evidence are all evaluated. There is substantial evidence to support the evaluation of the use of ondansetron in this practice setting. The setting of this project is Atlanticare obstetric unit where current practice dictates the administration of ondansetron prior to all cesarean section procedures. This project will evaluate de-identified data which will require few resources and have minimal to no impact on daily operations at this site. Based on the criteria laid out in phase three of the Stetler Model, the decision can be made for this project to move on to phase four (Stetler, 2001).

Phase four of Stetler's model is where the results are translated and implemented for the project. In this retrospective study, de-identified data will be provided by the site IT department of elective cesarean section patients undergoing a spinal anesthetic. There are three ways of

implementation, direct instrumental, cognitive, and symbolic use. For this project, cognitive use will be employed to better understand and appreciate the relationship of ondansetron administration, specifically the timing of the dose, and hypotension in spinal anesthesia. The method will also be considered in relation to informal/formal and direct/indirect. This project will be considered formal with indirect evaluation of aggregate patient data. This will require IRB approval prior to implementation (Stetler, 2001).

Phase five of Stetler's model is the evaluation phase. During this phase, the data can be evaluated in a formal/informal manner and can be accomplished on an individual or institutional level. This project will consider a formal evaluation at the institutional level. Evaluation of the data will review actual implementation and results of the project, while also summarizing phase one outcomes and goal results (Stetler, 2001). This phase concludes with official decisions on either a new best practice or continuation with the current status quo based on the results.

Theoretical Framework

The theoretical framework for this study is the Theory of Unpleasant Symptoms (TOUS). TOUS involves three major concepts. These concepts consist of symptom(s) of the patient, influencing factors, and performance outcomes (Smith & Liehr, 2013)

The symptoms concept is identified by four different areas. These areas consist of timing, intensity, quality, and distress. Spinal induced hypotension is an objective symptom which is associated with a variety of subjective symptoms. These symptoms can include nausea, vomiting, dizziness, and dyspnea (Miller & Pardo, 2018). The timing, intensity, quality and distress can vary depending on the severity of hypotension as well as how quickly it is treated.

The influencing factors are broken down into three distinct categories. Physiological, psychological, and situational factors make up these categories (Smith & Liehr, 2013). This

study aims to alter the physiological factor associated with the symptom of spinal hypotension. This will be accomplished through the evaluation of using ondansetron to avoid the physiological factor of hypotension from spinal anesthesia.

Performance outcomes can involve the impact of the symptom on the patient's ability to function physically (Smith & Liehr, 2013). Regarding this project, not only does this ability to function affect the patient, but it can also affect the baby as well. As stated above, untreated spinal induced hypotension can lead to worsening of symptoms and potential cardiovascular collapse in the parturient (Miller & Pardo, 2018). This can also lead to unwanted fetal side effects (Reynolds & Seed, 2005).

Methods

Setting

The site's OB department was the setting for this project. The site is a general medical and surgical facility that provides care to an underserved population. The OB department has 10 inpatient beds, four triage rooms, and two OR suites available. The site is also considered a teaching hospital and performs an estimated 900 cesarean sections a year.

Participants

Aggregate data was abstracted and de-identified by the site IT Dept. for all full-term maternal patients who have undergone elective cesarean section and received prophylactic ondansetron prior to spinal anesthesia. Exclusion criteria included all patients who underwent non-elective/emergent cesarean section, who received continuous phenylephrine infusion, and who did not receive spinal anesthesia. Aggregate de-identified data included cases during a one-year time frame (01/01/2020 – 12/31/2020) that meet the criteria.

Intervention

The retrospective data analysis evaluated the timing of administration of ondansetron and how it directly affects post-spinal anesthesia BP change scores and total vasopressor usage. Data at the patient level that was eligible for analysis was categorized into one of three groups based on the timing of ondansetron administration in relation to spinal administration. Aggregate de-identified data was provided by the site IT department.

Project Implementation

Institutional Review Board (IRB) approval was obtained from The University of Pennsylvania and from Atlanticare. A request to the site IT department for de-identified data abstraction was placed with the following parameters. Inclusion criteria, all anesthesia records and medication administration records (MAR) data for scheduled cesarean sections during the year 2020. Exclusion criteria, all non-elective or emergency cesarean sections, patients who received a phenylephrine drip/infusion, patients who did not receive prophylactic ondansetron, patients who have an allergy to ondansetron, patients who did not receive spinal anesthesia. Data requested included timing of prophylactic ondansetron administration, timing of spinal administration, patient demographics including age, race, ethnicity, weight, height, BMI, patient health history, blood pressure values at four specific time periods (pre-spinal administration blood pressure, 5,15,and 30 minutes post spinal), total ephedrine and phenylephrine used for the procedure.

De-identified Variable Data

The independent variable for this project was the timing of ondansetron administration prior to spinal anesthesia administration. Administration timing was categorized as follows: Group one (G1) was ondansetron administration ≤ 15 minutes of spinal administration; Group two (G2) was ondansetron administration > 15 minutes and ≤ 30 minutes of spinal

administration; Group three (G3) was ondansetron administration > 30 minutes from spinal administration.

The formula for categorizing the independent variable was: [spinal administration time – ondansetron administration time]. Upon determination of total time between procedures, patient level data were placed into one of the three groups accordingly.

There were two dependent variables evaluated in this project. The first dependent variable was blood pressure, pre- and post-spinal administration. The second dependent variable was the total amount of vasopressor usage during the procedure.

Blood pressure value data from four different time periods was included, including values for systolic BP, diastolic BP, and mean arterial pressure. The first time period was blood pressure value prior to spinal administration (baseline). The second BP value was five minutes post spinal administration. The third BP value was at 15 minutes post spinal administration. The fourth BP value was at 30 minutes post spinal administration.

Total vasopressor usage data (ephedrine and phenylephrine) was included for the entire procedure. Phenylephrine was presented in microgram (mcg) totals. Ephedrine was presented in milligram (mg) totals.

Other de-identified data presented included demographics and patient characteristics. This included age, race, ethnicity, weight, height, BMI, and patient health history with a focus on preeclampsia, gestational diabetes, and hypertension.

Data from the site was initially evaluated for errors and contained 298 patients. Of the 298 patients, 222 were excluded due to receiving a phenylephrine infusion leaving 76 patients. Three patients were excluded for being emergency cesarean sections leaving 73 patients. Seven

patients were excluded for not receiving ondansetron prior to spinal administration leaving 66 patients contributing data for the analysis.

Pre-spinal MAP data was not included in the data received but pre-spinal BP was provided. Pre-spinal MAP was therefore calculated by the equation (0.333*(pre-spinal systolic blood pressure - pre-spinal diastolic blood pressure) + pre-spinal diastolic blood pressure).

Data Management

The de-identified data in excel from the site IT Dept. was stored on Matthew Rowley's University of Pennsylvania's School REDCap account. Access was available to authors as well as DNP faculty members involved in this project. De-identified data had a random identifier number randomly assigned to each data row representing a single patient in the dataset.

Data was kept on the secure REDCap server for long-term storage. Data will be stored until analysis and dissemination of the results or until August 30, 2021. Data will then be destroyed.

Analysis

Descriptive statistics were used to summarize blood pressure measurements, vasopressor use, and patient characteristics. Blood pressure measurements were measured in mean and standard deviations, demographics were measured in frequency, mean and standard deviation. Data was evaluated for normality using box plots and the Shapiro-Wilk test for normality via SPSS Inc. (Version #27, IBM). Ephedrine and phenylephrine totals did not show normality, while most changes in blood pressure did. Upon confirmation of a normal distribution and absence of outliers, blood pressure change scores were used to calculate the one-way ANOVA. For blood pressure change scores that were not found to have normal distribution the Kruskal-Wallis was used instead. Change scores were calculated by subtracting the post-spinal blood

pressure values from the pre-spinal blood pressures. The separate tests determined the significance value of the independent variable groups (time of ondansetron administration) and each dependent variable (blood pressure changes scores). Dependent variables were each evaluated independently (Laerd statistics, 2017) between the groups. Vasopressor data was found to not be normally distributed, thus the Kruskal-Wallis test was utilized (Laerd statistics, 2017).

Analysis also included statistical evaluation of the demographic data. This included the mean and total number for each group. This evaluation helped to conclude whether the three groups were similar demographically (Laerd statistics, 2017).

Results

Group Description

An aggregate data set was used for the project that included data from 66 records. Groups included women with mean age of 31 years, predominantly white (40.9% [n=27]) and African American (31.8% [n=21]). The group was predominantly non-Hispanic (80.3% [n=53]). The total group ASA status was 74.2% ASA II, 24.2% ASA III, and 1.5% ASA I (See Table 2).

Records were grouped by Ondansetron administration timing to form group level data for the analysis. For detailed demographic descriptions see Table 2. Patients were placed into 3 groups: ondansetron administration ≤15 minutes (n=24), ondansetron administration >15 or ≤ 30 minutes (n=24) and ondansetron administration >30 mins (n=18).

One-Way ANOVA/Kruskal-Wallis for Changes in BP

A one-way ANOVA test was done to determine if the delivery timing of ondansetron had an effect on change in blood pressure. Test results are presented based on the F test statistic value and equivalent p-value. Overall, there were no statistically significant differences in change in blood pressure outcomes based on timing of ondansetron administration. The Kruskal-Wallis test

also showed no significant difference between the groups that were not normally distributed. See Table 3 for a complete list of values between groups. See table 5 for a complete list of blood pressure descriptives.

Kruskal-Wallis Test

A Kruskal-Wallis test was done to determine if the delivery timing of ondansetron had an effect on vasopressor usage. Visual inspection of boxplots show that distributions for both phenylephrine and ephedrine were not similar. The mean rank was not statistically significant for total ephedrine x2(3) =1.706 p = .426 and phenylephrine x2(3) = 5.739 p = 0.57 (Table 4). See Table 6 for average vasopressor totals.

Discussion

Summary

Although no significant values were found in the results of the data, there were notable differences in the results between the groups regarding changes in BP and Vasopressor usage. Overall changes in systolic, diastolic, and MAP showed G1 with the lowest decrease in BP in every time period except for 15 minutes post spinal, in which G2 had a higher systolic and MAP. G3 change scores were higher in all categories across all three time periods.

No significant values were found in the results of the Kruskal-Wallis test on vasopressor usage, however notable differences between the groups were seen. Average ephedrine usage was higher in G3 compared to G1 and G2. Similarly average phenylephrine administration was also higher in G3.

While overall results were considered not significant, the noted differences between the three groups is apparent. G3 had increased change/drop in BP over all 3 time periods compared

to G1 and G2. G3 also had the highest average vasopressor usage compared to G1 and G2. This is likely due to the drop in ondansetron peak plasma concentrations over time.

Peak plasma concentrations of 4mg of zofran after 5 minutes is around 65 ng/ml (EMC, 2020). Peak plasma concentrations drop to about 42.9 ng/ml after 10 minutes from IV administration (PDR, 2021). As time between administration of zofran and spinal administration increases, peak plasma concentrations of zofran are expected to decrease. The affects of zofran on inhibition of the BJR are likely to diminish, which may explain why G3 had greater average changes/drop in BP and increased average vasopressor usage compared to G1 and G2.

Limitations

Although results point toward ondansetron having a more positive affect in G1 and G2 limitations of this study may have affected statistical significance. These project groups consisted of smaller sample sizes and were not perfectly equal in number. Further projects may benefit with larger sample sizes per group as well as equal group numbers.

Another limitation that this project did not take into consideration is the average amount of crystalloid administered per group. Differences in crystalloid amount may have altered BP results per group in either direction. This may have had unknown effects on our results.

This project consisted of a retrospective de-identified data analysis. Further studies into this phenomena would benefit from RCT's to gain a better understanding of the affects of ondansetron on BP and vasopressor usage. An RCT would be the optimal study design to answer this question.

Implications for Practice/Policy

At this time our project cannot recommend a policy change for this site due to the lack of statistically significant results. However, positive benefits of administering ondansetron within

30 minutes of spinal administration can be seen in the data. This project does recommend further exploration of benefits either through a larger scale retrospective data analysis or through a research based RCT. Due to the vulnerable population at hand, aggregation of data from multiple hospitals would be recommended over utilizing a RCT.

Further studies into this subject could be a benefit to this site. Considering the results of the data, administering ondansetron within 30 minutes may not only provide higher quality patient care, but could also result in higher cost efficiency as well. Lower average vasopressor usage could lower cost while also improving maternal/fetal outcomes through improved homeostasis of the mother.

Opportunities for Sustainability

Continued sustainability is dependent on further studies and analysis into the effects on the timing of ondansetron in relation to spinal anesthesia for cesarean section. Due to the lack of statistical significance in the results presented, no recommendation can be made for sustainability at this time. As stated before, this project would recommend further evaluation and larger scale studies into this subject.

Conclusions

This project evaluated through retrospective analysis of de-identified data the change in BP and total vasopressor usage of patients receiving ondansetron at different times in relation to spinal administration for cesarean section patients. Results of data analysis did not show statistical significance. However, differences between the groups are noted with G3 having greater changes/drops in average systolic, diastolic, and MAP along with increased average vasopressor usage compared to G1 and G2. Further investigation is recommended for this site to either evaluate a larger population in a retrospective study or conduct a RCT. Through further

evaluation, improved timing of ondansetron could result in improved homeostasis of the mother/infant as well as lower cost of care.

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References

Dang, D., & Dearholt, S. (2018). *Johns Hopkins nursing evidence-based practice: Model and guidelines*. Indianapolis, IN: Sigma Theta Tau International.

EMC, (2020, May 13). Ondansetron 2 Mg/ml solution for injection. Retrieved May 13, 2021, from https://www.medicines.org.uk/emc/product/6469/smpc#gref

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*, *24*(4), 335–343. https://doi.org/10.1016/j.ijoa.2015.08.012

Heesen, M., Klimek, M., Hoeks, S. E., & Rossaint, R. (2016). Prevention of Spinal Anesthesia-Induced Hypotension During Cesarean Delivery by. *Anesthesia and Analgesia*, *123*(4), 977–988. https://doi.org/10.1213/ANE.0000000000001511

Laerd Statistics (2017). Three-way ANOVA using SPSS Statistics. *Statistical tutorials and software guides*. Retrieved from https://statistics.laerd.com/

Marashi, S. M., Soltani-Omid, S., Soltani Mohammadi, S., Aghajani, Y., & Movafegh, A. (2014). Comparing Two Different Doses of Intravenous Ondansetron With Placebo on Attenuation of Spinal-induced Hypotension and Shivering. *Anesthesiology and Pain Medicine*, *4*(2), e12055. https://doi.org/10.5812/aapm.12055

Miller, R. D., Pardo, M., & Stoelting, R. K. (2018). **Basics of anesthesia**. Philadelphia, PA: Elsevier/Saunders.

Moher, D., Hopewell, S., Schulz, K., Montori, V., Gøtzsche, P., Devereaux, P., Altman, D. (2010, August). CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. https://www.sciencedirect.com/science/article/pii/S0895435610001034

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

Ortiz-Gómez, J. R., Palacio-Abizanda, F. J., Morillas-Ramirez, F., Fornet-Ruiz, I., Lorenzo-Jiménez, A., & Bermejo-Albares, M. L. (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

PDR. (2021). Ondansetron Hydrochloride - Drug Summary. Retrieved May 10, 2021, from https://www.pdr.net/drug-summary/Zofran-Injection-ondansetron-hydrochloride-243

Ryu, C., Choi, G., Park, Y., & Kang, H. (2019, January). Vasopressors for the management of maternal hypotension during cesarean section under spinal anesthesia: A Systematic review and network meta-analysis protocol. Retrieved September 22, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6344174/

Shabana, A., Elkholy, N., Mohamed, A., & Abdel Hamid, M. (2018). Effect of ondansetron on hypotension and bradycardia associated with spinal anesthesia during cesarean section. *Menoufia Medical Journal*, *31*(1), 12–17.

Šklebar, I., Bujas, T., & Habek, D. (2019, June). SPINAL ANAESTHESIA-INDUCED HYPOTENSION IN OBSTETRICS: PREVENTION AND THERAPY. Retrieved October 18, 2020, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6813480/

Smith, M. J., & Liehr, P. R. (Eds.). (2013). *Middle range theory for nursing : Third edition*. ProQuest Ebook Central https://ebookcentral-proquest-com.proxy.library.upenn.edu

Stetler C. B. (2001). Updating the Stetler Model of research utilization to facilitate evidence-based practice. *Nursing outlook*, *49*(6), 272–279. https://doi-org.proxy.library.upenn.edu/10.1067/mno.2001.120517

Tatikonda, C. M., Rajappa, G. C., Rath, P., Abbas, M., Madhapura, V. S., & Gopal, N. V. (2019). Effect of Intravenous Ondansetron on Spinal Anesthesia-Induced Hypotension and Bradycardia: A Randomized Controlled Double-Blinded Study. *Anesthesia, Essays and Researches*, *13*(2), 340–346. https://doi.org/10.4103/aer.AER_22_19

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 Caesarean Section: A Prospective, Randomized, Controlled, Double-Blind Study. *Anesthesiology Research and Practice*, *2015*, 158061. 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. *AANA Journal*, *85*(2), 113–122.

University of Oxford CEBM (2020, October 01). Critical Appraisal tools. Retrieved December 01, 2020, from https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools

Wang, M., Zhuo, L., Wang, Q., Shen, M.-K., Yu, Y.-Y., Yu, J.-J., & Wang, Z.-P. (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.

Warltier, D. C., Campagna, J. A., & Carter, C. (2003). Clinical Relevance of the Bezold–Jarisch Reflex. *Anesthesiology*, *98*(5), 1250-1260. doi:10.1097/00000542-200305000-00030

Yamano, M., Ito, H., Kamato, T., & Miyata, K. (1995, September 19). Characteristics of

Inhibitory Effects of Serotonin (5-HT)3-Receptor Antagonists, YM060 and YM 114 (KAE-393), on the von Bezold-Jarisch Reflex Induced by 2-Methyl-5-HT, Veratridine and Electrical Stimulation of Vagus Nerves in Anesthetized Rats. Retrieved July 12, 2020, from https://www.jstage.jst.go.jp/article/jphs1951/69/4/69_4_351/_pdf

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. *The Journal of International Medical Research*, *46*(2), 654–662. https://doi.org/10.1177/0300060517716502

Figures

Figure 1. PRISMA

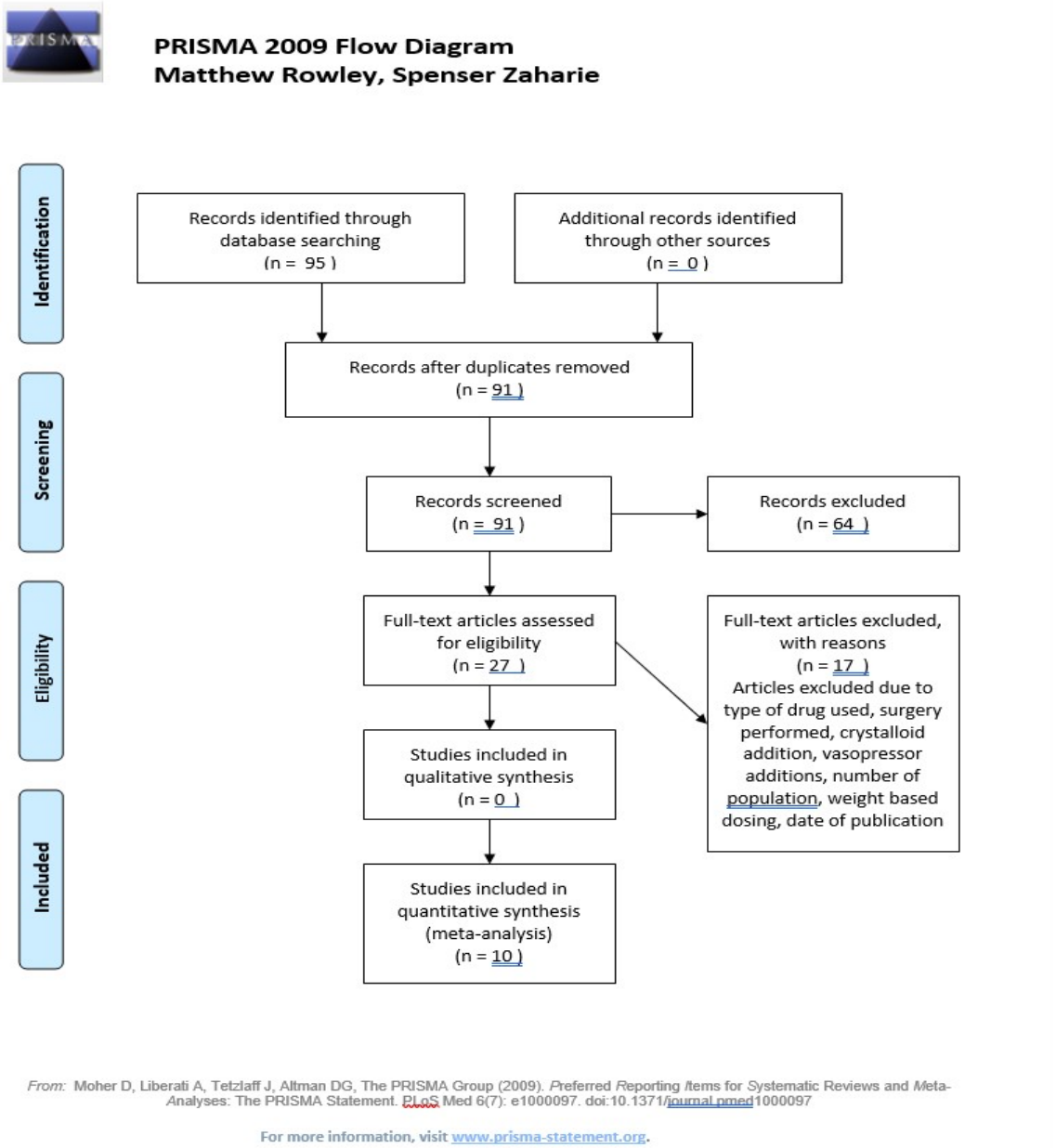


Figure 2. Stetler Model

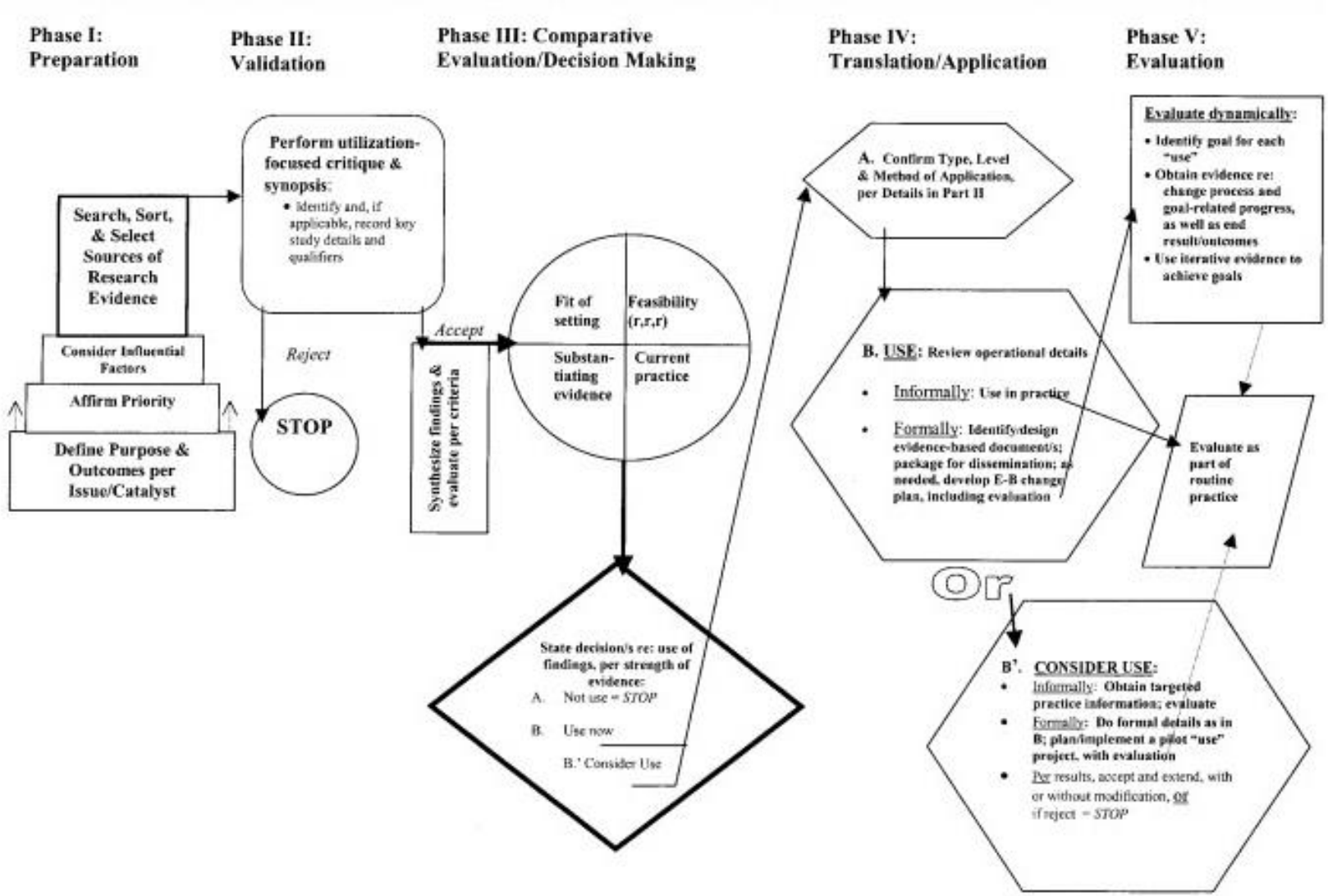
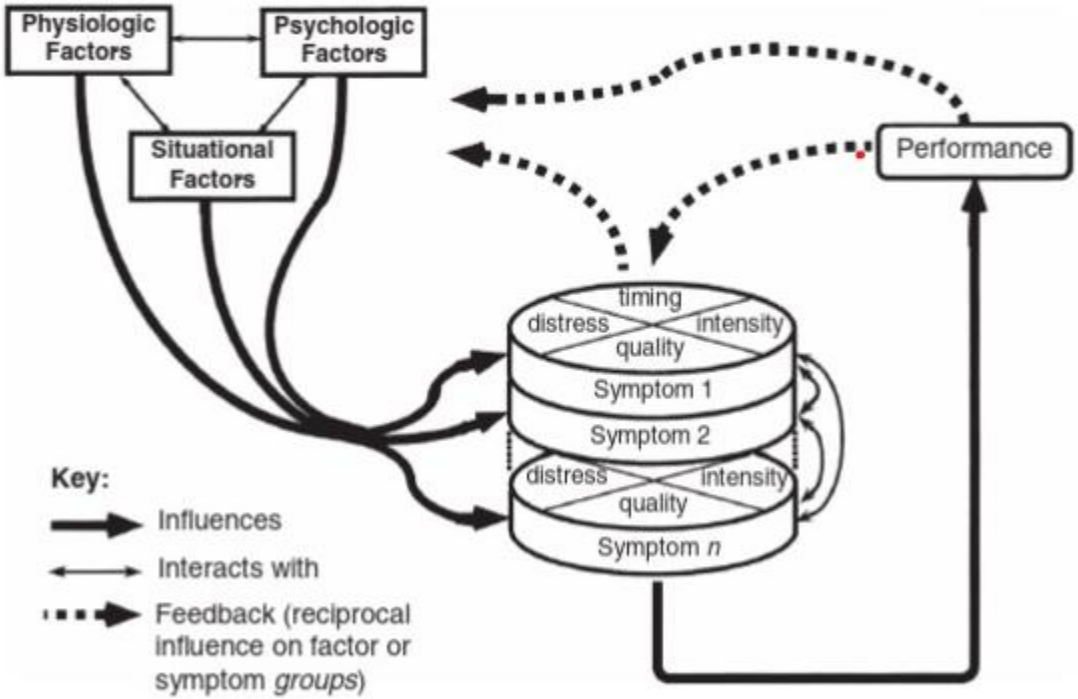


Figure 3. Theory of Unpleasant Symptoms



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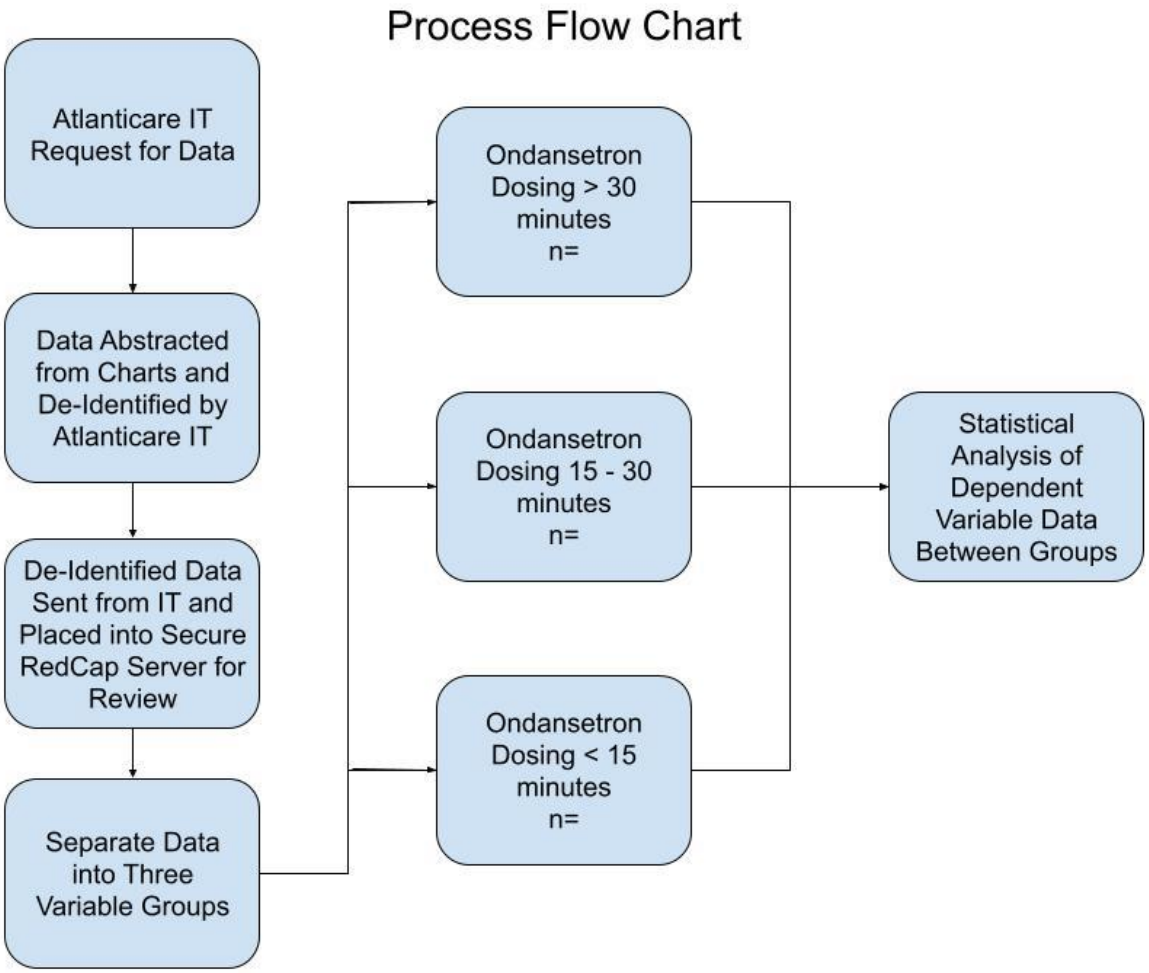
Descriptives

Figure 3 Process Flow Chart



Tables

Table 1. Table of Evidence

Citation or Study Number	Research Aim, Question, Hypothesis	Setting, Sample, and Sampling	Design	Variables and Measures	Findings	Level of Evidence	Conclusions
Gao et al., 2015	To investigate the effects of prophylactic Zofran on hemodynamic changes following spinal anesthesia.	Medline, Embase, Cochrane Library Databases searched for RCT's. 10 RCT's 6 of which were OB only. 863 patients included.	Meta-Analysis	Independent = Zofran, Dependent variable = hypotension.	Prophylactic zofran reduced incidence of spinal anesthesia-induced hypotension in OB/non-OB. RR (relative risk) 0.53 (95% CI 0.32 - 0.86) in OB, 0.16 (95% CI 0.05 to 0.51) non OB. Doses of Ephedrine and Phenylephrine required to treat hypotension reduced by zofran with mean differences -2.35mg (95% CI -4.14 to -0.55mg) and -31.16 μg (95% CI -57.46 to -4.87 μg).	Level IA	Results suggest prophylactic Zofran can alleviate hypotension, bradycardia, n/v caused by spinal anesthesia and reduce the amount of vasopressor drugs required.
Heesen et al., 2016	To determine whether 5-HT3 receptor antagonists, administered before the initiation of spinal anesthesia, mitigate hypotension.	PubMed, Embase, CINAHL, LILACS, CENTRAL, Clinicaltrials.gov, ISI WOS., randomized placebo-controlled double-blind trials studying preventive effect of 5-HT3 receptor antagonists included. Random effects model applied, risk ratio, weighted	Systematic Review and Meta-analysis and meta-regression.	Independent = Zofran 2-12mg, Dependent variable = hypotension.	Prophylactic 5-HT3 administration significantly reduced risk of hypotension in combined analysis of 17 trials. RR 0.54 (95% CI 0.36-0.81, I2 -79%). In OB trials RR was 0.52, 95% CI 0.30-0.88, I2 -87% (NNT 4). Non-obstetric studies 95% CIs were wide and included a clinically relevant reduction in risk of hypotension (RR 0.50, 95% CI 0.22-1.16, I2=66%). Contour-	Level 1A	5-HT3 antagonists are effective in reducing incidence of hypotension and bradycardia; effects are moderate and are only significant in subgroup of patients undergoing C-section. Effects in non-OB population not significant.

		mean difference with 95% confidence interval (CI) calculated. Primary outcome incidence of hypotension. 17 trials and 1604 patients.			enhanced funnel plots confirmed publication bias. Meta-regression showed significant zofran dose response in non-OB-only patients (β = -0.355, P=0.4). In combined and in OB-only analysis risk of bradycardia significantly reduced as was use of phenylephrine equivalents.		
Marashi et al., 2014	To investigate the effect of intravenous administration of zofran, which could attenuate spinal-induced hypotension, bradycardia, and shivering.	210 patients aged 20-50 years scheduled for spinal anesthesia. Randomly divided into 3 equal groups. Control group = NS, 6mg zofran group, 12mg zofran group 5 minutes before spinal anesthesia.	Randomized controlled trial.	Independent = zofran administration 6mg and 12 mg. Dependent = MAP, HR, shivering recorded before/after spinal anesthesia q 5 minutes during first 20 minutes surgery.	HR statistically different between experimental and control groups. 10 (14%) in control group had HR < 50 bpm requiring IV atropine compared to experimental group (P=0.02). In control group 12 (17%) patients had MAP < 80 mm Hg requiring vasopressors compared to experimental groups (P=0.04). No significant difference in MAP and HR between experimental groups (P=0.06). Incidence of shivering in control group 45% (32.70) statistically more than experimental group (P=0.02).	Level 1A	Administration of 2 different doses of IV Zofran 6mg/12mg significantly attenuates spinal induced hypotension, bradycardia, and shivering compared to a control saline group. Hemodynamic profiles/shivering in the 2 experimental groups were not statistically different.

Ortiz-Gómez et al., 2014	To study the effect of different doses of Zofran in obstetric patients.	Double-blind, randomized, placebo-controlled study, 128 healthy pregnant women scheduled for elective caesarean delivery, under spinal anesthesia.	Randomized Controlled Trial	Independent variable = 4 different Zofran doses 2/4/8mg and placebo. Dependent variable = hypotension. Demographic, OB, intraoperative timing and anesthetic variables assessed at 16 time points (BP, HR, O2 sat, n/v, ECG changes, skin flushing, discomfort, pruritus, vasopressor requirements.	No difference in number of patients with hypotension in placebo (43.8%), Zofran 2mg (53.1%), 4mg (56.3%), 8mg (53.1%) groups (P=0.77), neither the percentage of time points with systolic hypotension (7.3% placebo, 2mg 11.1%, 4mg 15.7%, 8mg 12.6%.) No differences between groups in ephedrine (P=0.11) or Phenylephrine (P=0.89) requirements and the number of patients with adverse s/e. Difference in ephedrine dosing amount was noted in chart...	Level 1B	Prophylactic zofran had negligible effect on incidence of hypotension in healthy parturients undergoing spinal anaesthesia with bupivacaine and fentanyl for elective caesarean delivery.
Shabana et al., 2018	To evaluate the efficacy of zofran during spinal anesthesia for c-section in overcoming the associated n/v,	100 parturients scheduled for elective cesarean section randomly allocated into two groups. Group 1 Zofran 4 mg, Group 2 received NS.	Prospective, RCT, double blind study.	Independent variable = 4mg zofran. Dependent variable = BP, HR, n/v, shivering,	Decreases in systolic arterial pressure were significantly lower in group 1 then group 2. Group 1 had significantly less requirement for vasopressors (P= 0.005). needed lower dose of vasopressor (P=0.01), and	Level 1A	Conclusion in parturient women undergoing elective cesarean section, intravenous 4mg zofran significantly decreased the hypotension, HR fluctuation, and vasopressor doses used.

	bradycardia, and hypotension.			vasopressor requirements, Apgar score at 1 and 5 min.	lower incidence of n/v (P=0.03). Decrease in HR was significantly lower in group 1 then Iafter spinal anesthesia administration) at 20 min , and 50 min Decrease in MAP lower in group I then II just after spinal anesthesia.		

Tatikonda et al., 2019	To study the effect of IV ondansetron on hypotension and bradycardia induced by spinal anesthesia.	140 ASA class I-II patients that were scheduled for infraumbilical surgery were assigned into two groups by a computer-generated random number table	Double Blind RCT	IV- Ondansetron DV- Hypotension, bradycardia, and shivering	Four patients in Group B and no patients in Group A experienced bradycardia No difference in hemodynamics (SBP, DBP, and MAP) between both Group A and B 19 patients in Group A and 33 in Group B required ephedrine with	IA	Prophylactic use of ondansetron reduced the need for ephedrine in patients receiving spinal anesthesia, and did not have an effect on bradycardia.
Trabelsi et al., 2015	Investigate the use of IV ondansetron for prophylaxis of hypotension after	80 ASA class I primapare parturients undergoing caesarean section were randomly assigned to	Double blind RCT	IV- Ondansetron DV- Hypotension	Less patients in the ondansetron group experienced hypotension as compared to those in the S group: 15 (37.5%) and 31 (77.5%)	IB	Study showed that prophylactic ondansetron had a significant effect on the incidence of hypotension in healthy parturients undergoing spinal anaesthesia

	spinal anesthesia in parturients scheduled for elective caesarean section and its consequences on newborn parameters	two groups using a computer generated random sequence			(P<0.001). Thus, the average consumption of ephedrine intraoperatively was 5.10 ± 7.78 mg in group O while it was 12.90 ± 9.27mg in group S with a significant difference . Bradycardia was seen in 6 patients in the ondansetron group, and was more frequent in the saline group,15 cases, Atropine administration in group S was 0.12 ± 0.22mg. Yet, no atropine was required in group O. Apgar scores in group O were higher than those in group S		with bupivacaine and sufentanil for elective caesarean delivery.
Tubog et al., 2017	The purpose of this review is to conduct a comprehensive meta-analysis of randomized controlled trials (RCTs) using intravenous (IV) ondansetron in reducing the incidence of	Literature search included MEDLINE, Google Scholar, CINAHL, and The Cochrane Review Database. RCTs of prophylactic ondansetron (any dose) vs placebo or other interventions administered before	A Systematic Review and Meta-Analysis	IV-Ondansatron DV-Hypotension and bradycardia	**Bradycardia**. 11 of the 13 RCTs had patients that experienced bradycardia in the placebo group, the treatment group or groups, or both. Two of the 13 studies reported statistically significant differences. Marashi et al. and Trabelsi et al. saw attenuation of spinal anesthesia-induced bradycardia in patients that received ondansetron. One of	1A	The results support the hypothesis that administration of IV ondansetron, 5 minutes before the placement of local anesthetic into the subarachnoid spa, helps to attenuate SIH and bradycardia

	hypotension and bradycardia associated with spinal anesthesia	neuraxial blockade, in all types of surgery that use spinal anesthesia as the primary anesthetic technique were included. MESH terms: ondansetron, hypotension, spinal-induced hypotension, maternal hypotension, bradycardia, and spinal anesthesia			these studies evaluated 6-mg and 12-mg doses, and the other study assessed a 4-mg dose. Meta-analysis of the pooled data showed that ondansetron reduced the risk of bradycardia by a relative 69% Maternal Hypotension. Nine RCTs reported the incidence of hypotension during elective cesarean delivery. Of these, 5 studies showed a significant reduction in hypotension compared with placebo. Pooled analysis of the 9 RCTs showed that IV ondansetron attenuated maternal hypotension Heterogeneity was lower compared with the all-procedure meta-analysis I2 = 68% vs. I2 = 73%. Four trials in the nonobstetric setting looked at the administration of IV ondansetron before spinal anesthesia. The pooled data showed that pretreatment of IV ondansetron was not associated with a decrease in the incidence of hypotension.		
Wang et al., 2014	Compare the efficacy of different doses of ondansetron preloading combined with rapid crystalloid	150 ASA class I-II primiparous and parturient women were selected at the Wuxi Maternal and Child Health Hospital. Participants were	Double-blinded RCT	IV Ondansetron administration of 2mg, 4mg, 6mg, 8mg DV	Compared with group S, the incidence of maternal hypotension was obviously but not significantly reduced in groups O2 and O8 , but significantly reduced in groups O4 and O6	IB	Prophylactic administration of 4 mg of ondansetron was the optimal dose to prevent hypotension during cesarean delivery.4

	coloading on reducing maternal hypotension during cesarean delivery. Also assessed the effects of different doses of ondansetron preloading on maternal nausea, umbilical venous pH, partial pressure of carbon dioxide (Pco2), bicarbonate (Hco3 -) and base excess in extracellular fluid (BEecf), and neonatal outcome after delivery.	randomly assigned to one of five groups using computer generated codes.		Hypotension, maternal nausea, umbilical venous pH, PCO2, HCO3 and base excess in extracellular fluid and neonatal outcome after delivery	The incidence of nausea in groups O2, O4, O6, and O8 was significantly lower than that in group S ($P < 0.05$) No bradycardia or vomiting were observed in groups O4, O6, and O8, while one and two women in groups S and O2 had bradycardia or vomiting The use of phenylephrine in group O4 was significantly less than that in group S There were no significant differences in Apgar scores at 1 and 5 min after delivery or birth weight among the five groups The gas analysis results showed that there were no significant differences in pH, Pco2, PO2, Hco3 -, or base excess		
Zhou et al., 2018	To investigate the efficacy and safety of ondansetron during cesarean section under spinal anesthesia	The Cochrane Library, PubMed, MEDLINE, and Web of Science were used to search for RCTs where ondansetron was given for spinal anesthesia for cesarean section.	Meta-Analysis	IV- Ondansetron DV- Hypotension	21 RCTs were used. Meta-analysis showed that ondansetron group had a decreased rate of nausea/vomiting P<0.00001 and bradycardia P=0.006 than the placebo group during cesarean section under spinal anesthesia]. There were no	1C	Ondansetron can effectively reduce the incidences of nausea, vomiting, and bradycardia during spinal anesthesia for cesarean section, and its safety is relatively good. Because of the small sample size of this study, this conclusion remains to be confirmed by

		Search terms included “randomized controlled trial,” “controlled clinical trial,” “cesarean section,” “ondansetron,” “epidural,” “spinal”			differences of pruritus, hypotension (N=362), or shivering during cesarean section while under spinal anesthesia (RR=0.92, 95% CI (0.83, 1.02), RR=0.72, 95% CI (0.50, 1.06), and RR=0.89, 95% CI (0.71, 1.11).		studies with a larger sample size and multi-center studies.

Table 2. Demographic Data

DEMOGRAPHIC STATISTICS

	G1 (n=24)	G2 (n= 24)	G3 (n=18)
AGE (MEAN/SD)	30.5 +/- 6.269	30.3 +/- 6.091	32.3 +/- 5.531
ASA STATUS (%[N])			
ASA 1	0% n=0	4.2% n=1	0% n=0
ASA 2	75% n=18	75% n=18	72% n=13
ASA 3	25% n=6	21% n=5	28% n=5
RACE (%[N])			
WHITE	45.8% n=11	33.3% n=8	44.4% n=8
BLACK/AFRICAN AMERICAN	33.3% n=8	41.7% n=10	16.7% n=3
ASIAN/PACIFIC	4.2% n=1	4.2% n=1	5.6% n=1
ASIAN INDIAN	4.2% n=1	0% n=0	5.6% n=1
CHINESE	0% n=0	4.2% n=1	0% n=0
OTHER RACE	12.5% n=3	16.7% n=4	27.8% n=5
ETHNICITY (%[N])			

Non-Hispanic	87.5% n=21	75.0% n=18	77.8% n=14
Mexican	4.2% n=1	4.2% n=1	5.6% n=1
Puerto Rican	8.3% n=2	4.2% n=1	5.6% n=1
Central-South American	0% n=0	0% n=0	5.6% n=1
Other Hispanic	0% n=0	16.7% n=4	5.6% n=1
Weight (Mean/SD)	86.4 kg +/- 22.27	93.8 kg +/- 19.95	90.3 kg +/- 22.10
BMI(Mean/SD)	32.3 +/- 7.34	35.9 +/- 7.28	36.9 +/- 8.63
Hypertension	4.2% n=1	12.5% n=3	5.6% n=1
Preeclampsia	0% n=0	8.3% n=2	5.6% n=1
Gestational Diabetes	0% n=0	4.2% n=1	0% n=0

Table 3. One-Way ANOVA

ANOVA

		F	Sig.
Change in Blood Pressure Baseline - 5 Minutes Post Spinal Systolic	Between Groups	1.388	0.257
Change in Blood Pressure Baseline - 5 Minutes Post Spinal Diastolic	Between Groups		0.215*
Change in Blood Pressure Baseline - 5 Minutes Post Spinal MAP	Between Groups	1.354	0.266
Change in Blood Pressure Baseline - 15 Minutes Post Spinal Systolic	Between Groups		0.939*
Change in Blood Pressure Baseline - 15 Minutes Post Spinal Diastolic	Between Groups	0.558	0.575
Change in Blood Pressure Baseline - 15 Minutes Post Spinal MAP	Between Groups	0.472	0.626
Change in Blood Pressure Baseline - 30 Minutes Post Spinal Systolic	Between Groups		0.308*
Change in Blood Pressure Baseline - 30 Minutes Post Spinal Diastolic	Between Groups	1.873	0.162
Change in Blood Pressure Baseline - 30 Minutes Post Spinal MAP	Between Groups		0.621*

Notes: *Kruskal-Wallis Test Value

Table 4. Kruskal-Wallis Test

HYPOTHESIS TEST SUMMARY

	Null Hypothesis	Test	Sig.	Test Statistic	Decision
1	The distribution of Total Ephedrine Dose Used mg is the same across categories of Groups.	Independent-Samples Kruskal-Wallis Test	0.426	1.706	Retain the null hypothesis.
2	The distribution of Total Phenylephrine Dose Used mcg is the same across categories of Groups.	Independent-Samples Kruskal-Wallis Test	0.057	5.739	Retain the null hypothesis.

Table 5. Blood Pressure Descriptives

BLOOD PRESSURE DESCRIPTIVES

		N	Mean	Std. Deviation
CHANGE IN BLOOD PRESSURE BASELINE - 5 MINUTES POST SPINAL SYSTOLIC	≤ 15 minutes	24	0.17	16.730
	> 15 minutes and ≤ 30 minutes	24	5.33	23.450
	> 30 minutes	18	10.61	19.626
	Total	66	4.89	20.291
CHANGE IN BLOOD PRESSURE BASELINE - 5 MINUTES POST SPINAL DIASTOLIC	≤ 15 minutes	24	-3.71	21.523
	> 15 minutes and ≤ 30 minutes	24	0.54	26.425
	> 30 minutes	18	7.44	18.312
	Total	66	0.88	22.769
CHANGE IN BLOOD PRESSURE BASELINE - 5 MINUTES POST SPINAL MAP	≤ 15 minutes	24	-2.88	16.783
	> 15 minutes and ≤ 30 minutes	24	4.58	22.388
	> 30 minutes	18	6.28	19.535
	Total	66	2.33	19.825
CHANGE IN BLOOD PRESSURE BASELINE - 15 MINUTES POST SPINAL SYSTOLIC	≤ 15 minutes	24	1.50	19.113
	> 15 minutes and ≤ 30 minutes	24	-1.79	22.124
	> 30 minutes	18	2.33	16.168
	Total	66	0.53	19.341
	≤ 15 minutes	24	-0.71	19.666

Change in Blood Pressure Baseline - 15 Minutes Post Spinal Diastolic	> 15 minutes and ≤ 30 minutes	24	-0.71	19.947
	> 30 minutes	18	4.67	13.933
	Total	66	0.76	18.282
Change in Blood Pressure Baseline - 15 Minutes Post Spinal MAP	≤ 15 minutes	24	0.08	18.594
	> 15 minutes and ≤ 30 minutes	24	-3.13	19.398
	> 30 minutes	18	2.06	12.827
	Total	66	-0.55	17.407
Change in Blood Pressure Baseline - 30 Minutes Post Spinal Systolic	≤ 15 minutes	24	3.71	14.424
	> 15 minutes and ≤ 30 minutes	24	7.58	16.940
	> 30 minutes	18	6.67	21.077
	Total	66	5.92	17.156
Change in Blood Pressure Baseline - 30 Minutes Post Spinal Diastolic	≤ 15 minutes	24	4.71	17.213
	> 15 minutes and ≤ 30 minutes	24	3.79	15.970
	> 30 minutes	18	13.11	16.761
	Total	66	6.67	16.868
Change in Blood Pressure Baseline - 30 Minutes Post Spinal MAP	≤ 15 minutes	24	4.08	14.166
	> 15 minutes and ≤ 30 minutes	24	4.46	15.374

	> 30 minutes	18	9.83	15.459
	Total	66	5.79	14.947

Table 6. Vasopressor Descriptives

VASOPRESSOR **DESCRIPTIVES**

GROUPS		Total Ephedrine Dose Used mg	Total Phenylephrine Dose Used mcg
≤ 15 MINUTES	Mean	2.71	346.04
	N	24	24
	Std. Deviation	5.706	423.246
> 15 MINUTES AND ≤ 30 MINUTES	Mean	2.29	177.08
	N	24	24
	Std. Deviation	5.706	132.681
> 30 MINUTES	Mean	6.11	499.22
	N	18	18
	Std. Deviation	9.934	695.996
TOTAL	Mean	3.48	326.38
	N	66	66
	Std. Deviation	7.177	461.469

Appendix A

DNP Team and Project Implementation Form

University of Pennsylvania
School of Nursing
Doctor of Nursing Practice Program

DNP Team and Project Implementation Form

This form is to be completed by the student(s), institutional/organization project member(s), and school of nursing project lead and submitted for approval to the DNP Program Director.

Student Name: Matthew Rowley and Spenser Zaharie

Project Title: Does Administration Timing of Ondansetron, a 5-HT3 Receptor Antagonist, Affect Inhibition of the Bezold-Jarisch Reflex in OB C-section Patients Receiving Spinal Anesthesia

School of Nursing DNP Project Faculty Lead: Dr. Susan Renz

Institutional/Organization DNP Project Member(s): Nicholle Giberson

I hereby accept the following proposed project pending IRB approval (completed by student[s]):
Project Site: Atlanticare Regional Medical Center

Project Purpose: To determine whether the timing of ondansetron has a significant effect on vasopressor usage and hypotension in elective cesarean section patients receiving spinal anesthesia at ARMC

Project Activities: Retrospective chart review, analysis of evidence, and dissemination of results

Participants (Describe target group; approximate # in project): 2

Site(s) Support (Resources):Nicholle Giberson

Data Management Plan: Data will be stored on Matthew Rowley's University of Pennsylvania's School REDCap account. Access will be available to Spenser Zaharie, Dr. Susan Renz

Anticipated Start Date: 1/31/2021

Anticipated End Date: 4/30/2021

As a doctoral student member of this team, I agree to conduct the project to the best of my abilities with professionalism.

Student Signature: Spenser Zaharie

Student Signature: Matthew Rowley

Student Signature:

As an institutional/organization member of this project team, I agree to read and review all drafts of the project within a timely turnaround (approximately 2 weeks).

Team Member Signature: Nicholle Giberson

Contact Information (email and phone number):
Nicholle.Giberson@atlanticare.org (856)912-4828

Team Member Signature:

Contact Information (email and phone number):

Team Member Signature:

Contact Information (email and phone number):

Team Member Signature:

Contact Information (email and phone number):

As the School of Nursing DNP Project faculty lead, I agree to meet with the student(s) and consult throughout the project.

Faculty Lead Signature:

Contact information (email and phone number):

SREH2 @ nursing. upenn.edu 610-574-6246

APPROVED BY DIRECTOR, DOCTOR OF NURSING PRACTICE PROGRAM:

Director Signature:

Date Approved: 12/5/20

Appendix B

Project Charter

AIM
To determine optimal ondansetron administration timing to attenuate hypotension and vasopressor need in obstetric patients undergoing elective cesarean section.
PROBLEM
Up to 80% of non-pretreated cesarean section patients undergoing spinal anesthesia will present with maternal hypotension.
IMPORTANCE
Maternal hypotension can lead to cardiovascular collapse in the parturient, as well as decreased perfusion and APGAR scores for the infant. Research suggests that prophylactic ondansetron administration prior to spinal anesthesia can decrease the incidence of maternal hypotension. Through optimization of ondansetron timing greater attenuation of maternal hypotension and decreased vasopressor administration may be achieved. Due to retrospective chart audit methods proposed, there is no direct risks to patients for this project.
EXPECTED OUTCOMES
The expected outcome will be evaluation of the retrospective chart audit data. Data will be used to determine if there is significant variability in response to different ondansetron administration times.
MEASURES
Patient data will be taken from CERNER Power Chart. Patients will be separated into different groups based on ondansetron administration timing. Measures will include systolic, diastolic, and mean arterial blood pressure, as well as total vasopressor usage for the procedure. Data will be entered and double checked simultaneously by both Spenser Zaharie and Matthew Rowley.
RISKS/BARRIERS
Challenges may include getting Cerner Power Chart access for Spenser Zaharie, a non-employee at the site. Cohort discovery is a potential barrier to successfully completing the project but can be mitigated by consultation with Informatics at the site. Other risks include patient privacy and HIPAA violation with identifiable data aggregation. Data protection plans are in place. IRB guidance for HIPAA relative to the project will be attended to and maintained.
STAKEHOLDERS
Key stakeholders include all ARMC elective cesarean section patients without contraindications to ondansetron, ARMC anesthesia practitioners, and ARMC pre-operative RN's.

SCOPE	
In Scope:	Out of Scope:
All ARBC OB department patients receiving ondansetron prior to spinal administration prior to elective cesarean section, without vasopressor infusions.	ARMC OB patients having non-elective/emergent cesarean section procedures.
SCHEDULE	
IRB approval will be obtained by January 31st 2021. A two month chart review will be accomplished February 1st 2021 through March 31st 2021. Analysis will be conducted following chart audit through April 2021.	
PROJECT TEAM	
Matthew Rowley	Co-Lead
Spenser Zaharie	Co-Lead
Dr. Amy Sawyer	Project Faculty Consultant
Dr. Susan Renz	Project Faculty Lead
Dr. Nicholle Giberson	Clinical Coordinator ARMC

Appendix C

N853 Gantt Chart