Ondansetron Administration Prior to Subarachnoid Block in Cesarean Section: An Evidence-Based Practice Analysis

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Introduction

Subarachnoid block (SAB) is a preferred regional technique utilized by many institutions for caesarean section. A sensory block height of T5 is necessary for a successful caesarean under SAB.[1] Unfortunately, side effects often emerge related to the physiological changes as a result of sympathetic nervous system inhibition. Current research suggests up to 55%-90% of parturients experience extended block height resulting in hypotension and bradycardia.[1,2] There is a reduction in cardiac output due to a decrease in systemic vascular resistance and venous pooling. Similarly, the shift of cardiac autonomic balance toward parasympathetic stimulation causes bradycardia and activation of left ventricular mechanoreceptors due to a decreased ventricular volume.[2] The mechanism is known as the Bezold-Jarisch reflex (BJR).

Research indicates hypovolemia stimulates the exaggerated response of the Bezold-Jarisch reflex. Mechanoreceptors located within the cardiac walls are thought to cause bradycardia and hypotension in relation to the hypovolemia and venous pooling of the SAB.[2] Preloading with IV fluid prior to the administration of an SAB is often utilized to attenuate hypotension, but with inconsistent results. Research proposes serotonin is an important mediator correlated with stimulating the BJR. Literature suggests 5-HT3 antagonists can reduce the BJR and attenuate hypotension and bradycardia.[1,2] Animal studies have found dependent factors that trigger the BJR include: decreased blood volume and peripheral 5-HT3 receptors located in the intracardiac vagal nerve endings. [2] It has been proposed that ondansetron, a 5-HT3 receptor antagonist often utilized for its' antiemetic effects, could be utilized to block the Bezold-Jarisch reflex.

Purpose

Bradycardia and hypotension in the parturient can lead to an exaggerated uteroplacental insufficiency and detrimental fetal effects. Nausea is an unpleasant sensation which can reduce patient satisfaction. The purpose of this review is to examine the effectiveness of ondansetron administration prior to SAB in reducing hypotension, bradycardia and nausea in parturients undergoing cesarean section.

Methodology

A PICO format guided the clinical question. PICO parameters included: P (patient population) = patients undergoing scheduled cesarean section with 0.5% bupivacaine SAB and preloaded with 10-20 ml/kg of IV fluid, I (intervention) = 4-8 mg IV ondansetron prior to SAB, C (comparison) = no IV ondansetron, O (outcome) = incidence of hypotension, bradycardia, and nausea.

Current literature was searched using the following electronic databases: Medline, PubMed, and The Cochrane Library. Publications were limited to those published in English between 2006 and 2016. To optimize search results, the following keywords were utilized individually or in combination: *Bezold-Jarisch reflex, bradycardia, bupivacaine, cesarean section, hypotension ondansetron, parturient, spinal anesthesia, subarachnoid block, Zofran.* Original keywords used for all databases were "ondansetron" and "spinal" yielding 187 articles. Supplementary search

terms utilized were “cesarean section” and “subarachnoid block” to reduce the search results to 50 articles. Studies included randomized-control trials (RCTs) examining the effect of ondansetron administration on the incidence of hypotension, bradycardia and nausea in the obstetric population undergoing SAB. Six RCTs met the study population definition and were selected. Each was reviewed to determine the efficacy of ondansetron administered prior to 0.5% bupivacaine SAB in patients undergoing scheduled cesarean section who were preloaded with 10-20 ml/kg of IV fluid.[3-8] The incidence of hypotension, bradycardia, and nausea were compared to a placebo group.

Literature Review

Sahoo et al.[3] conducted a randomized, double-blind, placebo-controlled trial to determine if ondansetron caused a reduction in spinal-induced side effects. The study included 52 ASA physical status I obstetric patients between 20 and 40 years of age undergoing elective cesarean section. Patients were randomly distributed into two groups to receive either IV ondansetron 4 mg diluted in 10 mL of normal saline or normal saline 10 mL. Preoperatively each patient was prehydrated with Lactated Ringer’s (LR) solution 20 mL/kg/h given over 30 minutes. The study solution was administered intravenously and 5 minutes later, 2 mL 0.5% bupivacaine was administered via SAB. Blood pressure and heart rate were documented at 2 minute intervals for 20 minutes beginning at the time of SAB administration, followed by 5 minute intervals until the end of surgery. Systolic blood pressure (SBP) <90 mmHg or diastolic blood pressure (DBP) <60 mmHg was treated with IV phenylephrine 50 mcg; heart rate (HR) <50 beats/minute was treated with IV atropine 0.3 mg. Eleven patients (42%) in the control group experienced a reduction in BP which required a vasopressor compared to two (7.7%) in the ondansetron group ($p = 0.009$). The incidence of nausea was also reduced in the ondansetron group (7.7%) compared to the control group (27%) ($p = 0.049$). There was not a significant difference in the incidence of bradycardia between the groups with two (7.7%) in the saline group and none (0%) in the ondansetron group becoming bradycardic ($p = 0.49$).

A study by Rashad and Farmawy [4] included 60 ASA physical status I-II women between ages 20 and 40 years scheduled for elective cesarean section. Patients were randomly divided into groups of twenty. The ondansetron group received 4 mg ondansetron diluted in 10 mL normal saline and the saline group received 10 mL normal saline injected IV over 1 min, 5 min prior to the subarachnoid block. All patients received a preload of LR solution 20 mL/kg given over 30 min. preoperatively. Spinal anesthesia was performed with 2 mL of 0.5% bupivacaine following the study drugs. MAP and HR were documented at 2 minute intervals for 20 minutes beginning at the time of SAB administration, followed by 5 minute intervals until the end of surgery. Hypotension was defined as a reduction of MAP by 20 percent from baseline, while bradycardia was defined by a HR less than 50 beat/minute. There was no statistically significant difference in the incidence of bradycardia, with 10% ($n = 2/20$) of patients in the control group and 0% ($n = 0/20$) in the ondansetron group suffering from bradycardia ($p = 0.49$). There was significant increase in the number of patients (35%, $n = 7/20$) requiring ephedrine for the treatment of hypotension in the control group compared to the ondansetron group (5%, $n = 1/20$) ($p = 0.044$). One (5 %) patient in the ondasetron group experienced nausea compared to seven (35%) in the control group ($p = 0.02$).

Wang et al.[5] studied 66 parturient women scheduled for elective caesarean sections. Participants were randomized into a control group or ondansetron group. Five minutes before SAB the ondansetron participants were injected with 4 mg of intravenous ondansetron and the control group was injected with 5 mL of saline. Spinal anesthesia was achieved with 2 mL 0.5% bupivacaine. After 2 minutes, maternal BP and HR were measured at 2 minute interval for 30 minutes. Following SAB, 10 mL/kg of LR solution was administered. Intravenous injection speed was adjusted to a maximal rate and the solution was rapidly infused within 10 minutes. Hypotension is defined as SBP less than 80% of baseline. If hypotension occurred, an IV bolus of 100 mcg of phenylephrine was given. Eighteen (56%) of the control group experienced hypotension compared to eight (25%) of the ondansetron group ($p = 0.011$). There was also a difference in the number who became nauseated with 34.4% ($n = 11/32$) of the control group compared to 6.1% ($n = 2/33$) of the ondansetron group reporting nausea ($p = 0.004$). There was no significant difference in the incidence of bradycardia; control 6.3%, $n = 2/33$ and ondansetron 0% ($p = 0.238$).

One hundred and fifty women with a single fetus scheduled for elective cesarean were enrolled in a randomized, double blind, dose-dependent study.[6] Patients eligible were 18 to 35 years of age and classified as ASA physical class I or II. The participants were randomly assigned to one of five groups of 30 women. Five minutes preceding SAB, the subjects were intravenously injected with 5 mL of saline or ondansetron 2 mg, 4 mg, 6mg or 8 mg diluted in 5 ml saline. Spinal anesthesia was performed 5 minutes after injection of IV ondansetron or saline. Two mL of 0.5% bupivacaine was administered to each patient for the SAB. The participant's BP and HR were measured in 2 minute intervals for 30 minutes. After SAB placement the intravenous infusion of LR was adjusted to maximal speed until 10 ml/kg was infused. If SBP fell to less than 80% of baseline, an IV phenylnephrine100 mcg bolus was administered. Eighteen (60%) participants who received saline experienced hypotension compared to 30 of the 89 (34%) who received either 4, 6, or 8 mg of ondansetron ($p = 0.017$). Ten (33.3%) of the control group reported nausea compared to 5.6% ($n = 5/89$) who received 4 to 8 mg of ondansetron ($p = 0.0003$). No patients in the 4 to 8 mg ondansetron groups became bradycardic while 6.7% ($n = 2/30$) of the control group did ($p = 0.06$).

Ortiz-Gomez et al.[7] enrolled 128 ASA physical status I patients scheduled for an elective cesarean section in a double-blind, placebo-controlled, randomized study. Women 20 to 45 years of age were randomly assigned to four groups of 32 subjects. Participants were placed into an ondansetron 2 mg, 4 mg, and 8 mg group or placebo group. Five minutes before SAB placement the anesthetist administered the study solution. Administration of the 0.5% bupivacaine dose was dependent on patient height following a specific formula: bupivacaine (mg)= height (cm) x 0.06, with fentanyl 20 mcg. Every participant was co-loaded with IV hydroxyrethyl starch (HES) 8 mL/kg. MAP, DBP and HR were recorded every 2 minutes for 15 minutes and then in 5 minutes intervals until the end of the procedure. Hypotension was defined as SBP <75% baseline. Treatment was initiated with ephedrine 10 mg or phenylephrine 50 mcg if maternal heart rate was >95 beats/minute. Bradycardia was defined as a maternal HR <45 beats/minute. IV atropine 0.01 mg/kg was initiated if HR was <45 beats/minute. No patients experienced bradycardia. Thirteen (41%) of the placebo group required a vasopressor for

treatment of hypotension compared to 20% (n = 13/64) of patients who received either 4 or 8 mg of ondansetron. This was not a statistically significant difference (p = 0.0506). A small number of patients experienced nausea, 1 of 32 in the placebo group (3.1%) and 4 of 64 in the ondansetron 4 or 8 mg groups (6.25%) (p = 0.66).

In a similar study by Mariniak et al.,[8] 72 patients ages 18 to 40 years, ASA physical status I or II, undergoing elective caesarean section were randomly assigned an ondansetron 8 mg group or placebo group. Participants were preloaded with 6% HES 10mL/kg. Following the infusion, the study solution was administered and SAB was achieved 5 minutes following injection. Spinal anesthesia was tailored to individual patient height with 0.5% bupivacaine and fentanyl 15 mcg. BP and HR were recorded every 2 minutes. Hypotension was determined as a 20% decrease in SBP or SBP <90 mmHg, and bradycardia was defined as HR less than 60 beats per minute. Hypotension was observed in both the ondansetron (39%, n =14/36) and placebo (44%, n = 15/34) groups with no statically significant difference (p = 0.84). No significant differences were noted in the incidence of bradycardia; ondansetron group, 2.8%, n = 1/36, compared to control group, 5.9%, n = 2/34 (p = 0.61) or the incidence of nausea; ondansetron group, 11%, n = 4/36, compared to control group, 12%, n = 4/34 (p = 1.0).

Author/Date	Incidence of Hypotension (Ondansetron)	Incidence of Hypotension (Control)	Incidence of Bradycardia (Ondansetron)	Incidence of Bradycardia (Control)	Incidence of Nausea (Ondansetron)	Incidence of Nausea (Control)	*Significant Outcomes
Sahoo et al, 2012	7.7% n = 2/26 p = 0.009*	42% n = 11/26	0% n = 0/26 p = 0.49	7.7% n = 2/26	7.7% n = 2/26 p = 0.049*	27% n = 7/26	Hypotension and nausea reduced
Rashad and Farmawy, 2013	5% n = 1/20 p = 0.044*	35% n = 7/20	0% n = 0/20 p = 0.49	10% n = 2/20	5% n =1/20 p = 0.02*	40% n = 8/20	Hypotension and nausea reduced
Wang, Zhuo, Shen, et al, 2014	25% n =8/33 p = 0.011*	56% 18/32	0% n = 0/33 p = 0.238	6.3% n = 2/32	6.1% n = 2/33 p = 0.004*	34.4% n = 11/32	Hypotension and nausea reduced
Wang, Zhuo, Wang, et al, 2014	34% n = 30/89 p = 0.017*	60% n =18/30	0% n = 0/89 p = 0.06	6.7% n = 2/30	5.6% n = 5/89 p = 0.0003*	33.3% n =10/30	Hypotension and nausea reduced
Ortiz-Gomez, 2014	20% n = 13/64 p = 0.0506	41% n= 13/32	0%	0%	12.5% n = 8/64 p = 0.25	21.8% n= 7/32	No significant differences
Marciniak, 2015	39% n = 14/36 p = 0.84	44% 15/34	2.8% n = 1/36 p = 0.61	5.9% n = 2/34	11% n = 4/36 p = 1.0	12% n = 4/34	No significant differences

*statistically significant difference

Conclusion

The objective of this evidence-based practice analysis was to determine if IV ondansetron administered prior to SAB would attenuate maternal hypotension, bradycardia and nausea. Six studies were reviewed; four of six concluded a reduction in hypotension and nausea. Of importance to note, each subject was adequately preloaded with either colloid or crystalloid 10-20 mL/kg and 0.5% bupivacaine was used in each study. There was no difference in the incidence of bradycardia in any of the studies.

The research reviewed had some inconsistences and included small sample populations. Differences in regards to IV fluid solution type and amount, timing of IV fluid loading and parameters for vital signs varied in the studies. Strengths of the current review include all studies were RCTs, utilized 0.5% bupivacaine and included IV loading. In a recent meta-analysis by Gao et al. they reported the overall incidence of nausea and vomiting was decreased along with the administration of vasopressor.[9]

A recently published review by Pellegrini suggests that co-loading of IV fluid rather than preloading appears to be effective in reducing spinal induced hypotension. Another body of evidence supports that the use of lower-extremity compression devices may play a role in the incidence of hypotension.[10] It is unknown if lower-extremity compression devices were used in the RCTs analyzed for this review. Spinal induced hypotension, bradycardia and nausea remain to be problematic for cesarean population receiving SAB. Although the current literature provides favorable evidence, better-designed and well-powered studies are needed to make clinical recommendations and fully conclude the efficacy in the use of ondansetron.

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