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Does prophylactic administration of ondansetron prior to spinal anesthesia decrease spinal-anesthesia induced hypotension in obstetric and non-obstetric patients?: a literature review

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DOES PROPHYLACTIC ADMINISTRATION OF ONDANSETRON PRIOR TO SPINAL ANESTHESIA DECREASE SPINAL-ANESTHESIA INDUCED HYPOTENSION IN OBSTETRIC AND NON-OBSTETRIC PATIENTS?: A LITERATURE REVIEW.

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ABSTRACT

Introduction: Neuraxial (spinal) anesthesia is a favored modality in the care of obstetric patients undergoing a cesarean-section (C-section). Spinal anesthesia is additionally popular as an alternative method for various surgical procedures in non-obstetric patients allowing practitioners to avoid potential risks associated with the use of general anesthesia. Spinal anesthesia-induced hypotension (SAIH) is a common side effect that presents status post-initiation of spinal anesthesia. The source of the hypotension produced after the initiation of spinal anesthesia is due to inhibition of the sympathetic nervous system (sympathectomy) and bradycardia caused by stimulation of the Bezold-Jarisch Reflex. A relatively new intervention that practitioners are using to mitigate the stimulation of the Bezold-Jarisch Reflex is the use of 5-HT3 receptor antagonists. Ondansetron is a 5-HT3 receptor antagonist implicated in decreasing the incidence and severity of SAIH.

Objective: The purpose of this literature review was to examine the efficacy of the prophylactic administration of ondansetron (5-HT3 receptor antagonist) before induction of spinal anesthesia in the attenuation of the incidence of SAIH. The hypothesis used in this research study was : Does Prophylactic Administration Of Ondansetron Prior To Spinal Anesthesia Decrease Spinal-Anesthesia Induced Hypotension In Obstetric And Non-Obstetric Patients":

Methodology: The current literature review attempts to identify recent studies on the use of prophylactic ondansetron before spinal anesthesia and its ability to decrease the incidence of SAIH. Databases which included: PUB-MED, Academic Search Premier, EBSCO Host, and Google-Scholar were searched for randomized control trials (RCTs) investigating the effects of ondansetron and its ability to attenuate SAIH. The principal outcome of the focus for this review

was the incidence of hypotension after the initiation of spinal anesthesia. PRISMA guidelines and the Cochrane Risk of Bias Tool influenced the design and data collection of this review. *Results:* Eleven studies (Five non-obstetric and six obstetric) consisting of 1,257 patients (non-obstetric n = 616, Obstetric n = 641) categorized by the American Society of Anesthesiology (ASA) class I-III were included in this review. Three out of five non-obstetric-group studies support the hypothesis of this literature review and concluded that prophylactic ondansetron administered before spinal anesthesia was effective in decreasing the incidence of hypotension compared to a placebo. Three out of six obstetric group studies also supported the hypothesis of this literature review and concluded that prophylactic ondansetron before spinal anesthesia was effective in decreasing the incidence of hypotension when compared to a placebo. *Discussion/Conclusion:* The results of this literature review show that the prophylactic administration of ondansetron before induction of spinal-anesthesia does not clearly inhibit stimulation of the BJR or significantly decrease the incidence of SAIH in obstetric and non-obstetric patients. Additional studies are needed focusing on uniformity in testing so there can be stronger correlations in comparing results, and thus more definitive conclusions can be made.

Keywords: Bezold-Jarisch reflex, Ondansetron, serotonin, spinal-anesthesia induced hypotension, 5-HT3 receptors.

INTRODUCTION

Neuraxial(spinal) anesthesia is a popular modality used for the management of obstetric patients undergoing cesarean section (C-Section). Hypotension is a familiar and predictable event anticipated in the obstetric patient undergoing spinal anesthesia (Hasanin, Mokhtar, Badawy, & Fouad, 2017). Complications that may arise in the mother and newborn as a result of Spinal Anesthesia-Induced Hypotension (SAIH) include nausea and vomiting and cardiovascular collapse in the parturient and decreased perfusion and acidosis in the fetus due to compromised uteroplacental blood flow as a result of maternal hypotension (Barash et al., 2017). Spinal anesthesia is also considered safe for use in the non-obstetric population for many procedures in patients who may be at increased risk of adverse events associated with the administration of general anesthesia. Furthermore, complications that may arise in the non-obstetric patient in response to SAIH include but are not limited to decreased perfusion of vital organs and tissues, and the potential for cardiovascular collapse (Nagelhout & Sass, 2018). The prevalence of hypotension found in the obstetric population is as high as 75% of cases and in the non-obstetric population prevalence is open for debate due to multiple factors but has been found as high as 70% in the elderly (Owczuk et al., 2015; Šklebar, Bujas, & Habek, 2019). The two main factors that influence the incidence of hypotension after initiation of spinal anesthesia are: first, how hypotension is defined, and second, the amount (dose) of Local Anesthetic (LA) administered intrathecally (Lee, George, & Habib, 2017). The definition of hypotension varies and can be confusing when trying to compare the incidence of hypotension reported among different studies. The literature has revealed that researchers have used as many as fifteen different definitions of hypotension in their studies (Klohr, Roth, Hofmann, Rossaint, & Heesen,

2010). Though a consensus definition of hypotension is not currently accepted, it is referenced most often in correlation with a patient's systolic blood pressure (Carpenter, Caplan, Brown, Stephenson, & Wu, 1992). Despite the variance amongst studies, the most common definition of hypotension used in the literature is a drop in baseline blood pressure of 20% or higher (Habib, 2012).

In reference to the incidence of hypotension being dependent on the amount of local anesthetic administered intrathecally. Using low-doses of Bupivacaine (5-7 mg) for the management of C-section via spinal anesthesia has been shown to reduce the severity of hypotension and the adverse effects of SNS depression (Roofthooft & Van de Velde, 2008). It is important to note that decreasing the amount of LA to decrease the severity of sympathectomy elicits undesired consequences such as the need for increased intraoperative analgesia requirement and slower onset and decreased duration of spinal block (Arzola & Wieczorek, 2011);(McNaught & Stocks, 2007). The increased analgesic requirement is a concern because many drugs used for intraoperative pain control can cause cardiac depression, possibly negating any benefit from decreasing the amount of LA administered intrathecally (Flood, Rathmell, & Shafer, 2015). Other factors that may also influence the frequency and severity of hypotension in patients undergoing spinal anesthesia are a result of a diverse population in reference to an individual patient's personal medical history, including comorbidities and the anesthesia technique administered (Tubog, Kane, & Pugh, 2017). In order to manage hypotension and to prevent the possible adverse complications that may arise as result, anesthesia providers have developed strategies to both prevent and treat SAIH. These strategies included using fluid preloading/co-loading to augment venous pressure, leg compression to optimize venous return, and positioning using left uterine displacement to prevent aortocaval compression of the great

vessels (Nagelhout & Sass, 2018) These modalities are still used today as part of the anesthetic management of SAIH. However, they are minimally effective in the treatment of SAIH, thus weakening the claim that aortocaval compression and venous pooling in the lower extremities are the primary causes of hypotension (Lee et al., 2017). Moreover, evidence from multiple studies has indicated that after initiation of spinal anesthesia, heart rate and stroke volume increase for the first 15 minutes, improving CO (Dyer et al., 2009; Langesaeter, Rosseland, & Stubhaug, 2008). During this same period, there is a significant drop in systemic vascular resistance (), underscoring the notion that a reduction of arterial tone is the probable source of hypotension (Langesaeter et al., 2008; Sharwood-Smith & Drummond, 2009). As a result, anti-hypotensive drugs (vasopressors) are popular and are the foundation for the management of SAIH (Barash et al., 2017)

The management of SAIH was the primary focus of anesthesia practitioners for an extended period. In response to additional information that has been made available on the processes that lead to SAIH, prevention once again is the focus. The Bezold-Jarisch Reflex (BJR) is suspected to be critical in cascading events that occur after spinal anesthesia, leading to bradycardia and hypotension (Flood et al., 2015). An immediate response with interventions aimed at remedying these adverse events of bradycardia and hypotension are essential; otherwise, cardiovascular collapse may ensue (Campagna & Carter, 2003). The BJR is a cardioinhibitory reflex controlled by unmyelinated (type-C) nerve fibers residing in the heart (Campagna & Carter, 2003; Flood et al., 2015). The BJR activates via agonism of peripheral serotonin 5-hydroxytryptamine (5-HT3) receptors (Martinek, 2004).

To prevent the stimulation of the BJR and, subsequently, the bradycardia and hypotension that follows, antagonism of peripheral 5-HT3 receptors has been a focus of exploration.

Ondansetron is a frequent agent used in anesthesia for prevention as well as treatment of postoperative nausea and vomiting. Ondansetron is also a 5-HT3 receptor antagonist and has been the most widely studied 5-HT3 receptor antagonist used to potentially attenuate SAIH and bradycardia (Tubog et al., 2017). This literature review of Randomized Control Trials (RCTs) recognized if the prophylactic administration of intravenous (IV) ondansetron before initiation of spinal anesthesia is effective in decreasing the incidence of hypotension.

The purpose of this literature review was to examine the efficacy of the prophylactic administration of ondansetron (5-HT3 receptor antagonist) before induction of spinal anesthesia in the attenuation of the incidence of SAIH.

METHODOLOGY

Research Hypothesis: The hypothesis used in this research study was : Does Prophylactic Administration Of Ondansetron Prior To Spinal Anesthesia Decrease Spinal-Anesthesia Induced Hypotension In Obstetric And Non-Obstetric Patients":

Literature Review: The databases, including PubMed, EBSCO Host, Google Scholar, and Academic Search Premier, were utilized without filters or language restrictions for studies conducted from 1992 and 2020 in the English language. The following [MeSH Terms] WERE used: (obstetric OR non-obstetric) AND (("Anesthesia, Spinal") AND (Hypotension) AND (Ondansetron). The bibliographies of articles were retrieved and utilized to identify potential studies for inclusion in this review. The Cochrane Handbook for Systematic Reviews helped to prevent/limit selection bias based on the methodological approach used in the studies screened for inclusion in this review (Higgins, Thomas, Cumpston, Li, & Page, 2019). The literature review design followed the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) flowchart(Moher, Liberati, Tetzlaff, & Altman, 2009). The initial search found 158 articles an additional nine articles found through bibliographies. After removing duplicates, 136 abstracts got screened for potential inclusion in the current study. One-hundred and twenty of these articles were immediately excluded based as they did not follow to the purpose of this literature review. Nine-teen articles were relevant to the purpose of this assessment, but only sixteen articles had a full-text available (See figure 1). The full-text articles additionally received an evaluation for the risk of bias (RoB) using the Cochrane RoB tool. To be included in the qualitative analysis, articles had to score a low RoB in at least five of the seven categories listed by Cochrane (see *Table 1).* Only eleven articles (5 non-obstetric, and six obstetric) were deemed to meet this standard and were included in the results section of this review (*see Tables 2 and 3*). Abstracts did not get included in this study. The Chi-Square test was used amongst the different studies to compare the incidence of hypotension between the ondansetron and placebo groups. A P-value of $\leqq 0.05$ signified to be statistically significant.

RESULTS

Eleven studies (Five non-obstetric and six obstetric) consisting of 1,257 patients (non-obstetric n = 616, Obstetric n = 641) categorized by the American Society of Anesthesiology (ASA) class I-III compromise this review (See Table 1). The purpose of the 11 studies was to determine if ondansetron, a 5-HT3-receptor antagonist, effectively attenuates SAIH through inhibition of the BJR, which activates via agonist of serotonin (5-HT3) receptors. The primary outcome of these studies' focus was the incidence of hypotension after prophylactic intravenous (IV) ondansetron was administered before spinal anesthesia compared to a placebo.

Non-obstetric Studies: Three out of the five non-obstetric-group studies reported that prophylactic ondansetron administered before spinal anesthesia was effective in decreasing the incidence of hypotension compared to a placebo (*See Table 2).* In their study of 106 patients, Baig et al. found that ondansetron 6 mg IV before spinal anesthesia significantly reduced the incidence of hypotension compared to a placebo (Baig, Shah, Khurshid, Abid, & Tariq, 2017). Only 4/53 or 7.5% of patients who were administered ondansetron developed hypotension compared to 15/53 or 28.3% of patients who received a placebo (P = 0.005) (Baig et al., 2017). In a study of 100 patients, Shah et al. found that ondansetron 8 mg IV before spinal anesthesia significantly reduced the incidence of hypotension compared to a placebo (Shah, Naqvi, & Abbas, 2019). In their study, 23/50 or 46% of patients receiving ondansetron developed hypotension compared to 36/50 or 72% of patients who received a placebo (P = 0.026). Marashi et al. .in a study of 210 patients found that ondansetron 6 mg and 12 mg of ondansetron IV given before spinal anesthesia significantly reduced the incidence of hypotension compared to a placebo (Marashi, Soltani-Omid, Soltani Mohammadi, Aghajani, & Movafegh, 2014). In their study, there were no patients who received ondansetron that developed hypotension compared to 12/70 or 17% of patients who received a placebo (P = 0.04)

In contrast, there were two among the non-obstetric-group studies included in this review that did not find ondansetron to be Statistically significantly effective in decreasing the incidence of hypotension compared to a placebo (*See Table 2).* Bommala et al., in a study of 60 patients, found that ondansetron 4 mg IV before spinal anesthesia did not sufficiently decrease the incidence of hypotension compared to a placebo (Bommala et al., 2019). In their study, 7/30 or 24.3% of patients who received ondansetron developed hypotension compared to 14/30 or 46% of patients receiving a placebo (P= 0.079) Tatikanda et al., in a study of 140 patients, also did not

find that 4 mg of ondansetron IV before spinal anesthesia significantly reduced the incidence of hypotension compared to a placebo (Tatikonda et al., 2019). In their study, they reported that 17/70 or 24.3% of patients given ondansetron developed hypotension compared to 23/70 or 32.9% of patients receiving a placebo ($P > 0.05$)

Obstetric studies: Three out of SIX studies obstetric group studies determined that prophylactic ondansetron before spinal anesthesia was effective in decreasing the incidence of hypotension when compared to a placebo (*See Table 3.*). Abbas et al., in a study of 100 patients, found that 4 mg of ondansetron IV before spinal anesthesia significantly decreased the incidence of hypotension when compared to a placebo (Abbas, Shah, & Naqvi, 2016). Their study found that 21/50 or 42% of patients given ondansetron exhibited hypotension compared to 34/50 or 72% of patients given a placebo ($P = 0.009$) (Abbas et al., 2016). Sahoo et al., in a study of 52 patients, reported that 4 mg of ondansetron IV before spinal anesthesia was successful in decreasing the incidence of hypotension when compared to a placebo (Sahoo, SenDasgupta, Goswami, & Hazra, 2012). In their study, they found that 2/26 or 8% of patients receiving ondansetron developed hypotension compared to 11/26 or 42% of patients who received a placebo ($P = 0.009$) Also, Trabelsi et al., in a study of 80 patients, found that 5 mg of ondansetron IV before spinal anesthesia was sufficient in decreasing the incidence of hypotension compared to a placebo (Trabelsi et al., 2015). In their study, they reported that 15/40 or 37.5% of patients who received ondansetron developed hypotension compared to 31/50 or 77.5% of patients who received a placebo ($P < 0.001$)

In contrast, there were 3 of the obstetric group studies that found that ondansetron administered IV before spinal anesthesia was not significantly successful in attenuating the incidence of hypotension when compared to a placebo (*See Table 3.*). Karacaer et al. in a study consisting of

104 patients reported that 8 mg of ondansetron IV before spinal anesthesia was not significantly effective in decreasing the incidence of hypotension compared to a placebo (Karacaer, Biricik, Ünal, Büyükkurt, & Ünlügenç, 2018). In their study, they found that 47/54 or 87% of patients administered ondansetron developed hypotension compared to 48/54 or 89% of the patients who received a placebo (P = 0.76) (Karacaer et al., 2018). Oofuvong et al., in a study comprised of 210 patients, found that 0.05 - .1 mg/kg of ondansetron IV before spinal anesthesia did not significantly decrease the incidence of hypotension when compared to a placebo (Oofuvong, Kunapaisal, Karnjanawanichkul, Dilokrattanaphijit, & Leeratiwong, 2018). In their study, they found that 60/71 or 84.5% of patients receiving .05 mg/kg and 53/72 or 73.6% of patients who received 0.1 mg/kg of ondansetron developed hypotension compared to 59/72 patients who received a placebo (P = 0.23) (Oofuvong et al., 2018). Terkawi et al., in a study of 86 patients, found that 8 mg of IV ondansetron administered before spinal anesthesia was not significantly efficient at decreasing the incidence of hypotension when compared to a placebo (Terkawi et al., 2015). Their study found that 26/44 or 59.1% of patients who received ondansetron developed hypotension compared to 25/42 or 59.5% of patients who received a placebo (P = 1).

Non-obstetric Studies incidence of hypotension: Incidence of hypotension in patients receiving prophylactic ondansetron in non-obstetric patients ranged from 0% – 46% compared to 17%-72% in patients receiving a placebo (*See Table 2.*). In the five studies reviewed in this group, all patients 15 mg of Bupivacaine intrathecal, and one study additionally used 25 mcg of fentanyl in combination with Bupivacaine Baig et al., Marashi et al., and Tatikonda et al. defined hypotension as a 20% decrease in MAP from baseline or a MAP less than 80mmHg. Bommala et al. defined hypotension as a 30% decrease in SBP from baseline or SBP less than 90 mmHg, and Shah et al. defined hypotension as a 20% decrease in SBP or SBP less than 90 mmHg). The

dose of ondansetron administered before spinal anesthesia also varied among the studies in this group ranging from 4 -12 mg (*See Table 2).*

Obstetric Studies incidence of hypotension: Incidence of hypotension in patients receiving prophylactic ondansetron in obstetric patients ranged from 8-87% to 42-89% in patients receiving a placebo (*See Table 3).* In the six studies reviewed in this group, patients were administered Bupivacaine intrathecal in doses ranging from 10-15mg. Also, 4/6 studies in this group administered narcotics in combination with Bupivacaine for spinal anesthesia (*See Table 3).* Karacaer et al., and Abbas et al. defined hypotension as a 20% decrease in SBP from baseline. Oofuvong et al. defined hypotension, as a greater than 30% decrease in MAP, Terkawi et al. defined hypotension as an SBP less than 90mmHg. Trabelsi et al. defined hypotension as a less than or equal to 20% decrease in SBP or less than 80 mmHg, and Sahoo et al. defined hypotension as an SBP less than 90 mmHg or DBP less than 60 mmHg. The dose of ondansetron administered before spinal anesthesia also varied in this group and ranged from 4-8mg (*See Table 3).*

DISCUSSION

The purpose of this literature review was to examine the efficacy of the prophylactic administration of ondansetron (5-HT3 receptor antagonist) before induction of spinal anesthesia in the attenuation of the incidence SAIH. The results of the current study are mixed regarding if the prophylactic ondansetron did decrease the incidence of SAIH. Nearly 50 % of the studies

included in this review reported no significant decrease in the incidence of hypotension in patients who received ondansetron compared to those patients who received a placebo. These findings diminish the results found in the six studies that concluded that ondansetron significantly decreased the incidence of SAIH compared to a placebo. The different studies show a significant amount of heterogeneity that may have played a factor in the individual results reported.

Implications of heterogeneity amongst studies: The two most important factors that influenced the incidence of SAIH were how hypotension was defined and how much LA was administered intrathecal (Lee et al., 2017). Focusing on these two factors in comparing the various studies included in this literature review highlights potential problems in drawing a definitive conclusion when assessing the results reported. In both the no obstetric and obstetric groups, we can see that hypotension was defined differently in both the percentage decrease from baseline and the unit of measurement assessed as some used Mean Arterial Pressure (MAP), while others used SBP (*See Table 2,3).* The dose of LA was the most congruent in the non-obstetric group as Bupivacaine 15 mg was the dose of LA used in all the studies included, with the only exception being that Bommala et al. added 25mcg of fentanyl to their LA (*See Table 2).* In the obstetric group, all but 2 of the studies used narcotics in combination with LA in their studies.

The impact of how hypotension was defined and how impacted the incidence of hypotension reported amongst the different groups included in this study is difficult to assess. It is reasonable to assume that the incidence of hypotension would be lower in a study that defined hypotension as a 30% decrease from baseline compared to a study that defined hypotension as a 20% decrease from baseline. Also, it is difficult to draw a definitive conclusion when comparing

the results of the reported studies when more than 1 unit of measure defined hypotension, for example, MAP vs. SBP.

The amount of LA administered intrathecal is conceptually easier to compare and draw conclusions on how it may affect the incidence of hypotension. The side effects of most anesthetic drugs, including LAs, are typically dose-dependent, primarily when used in combination with other agents. The addition of opioids to the LA can increase the incidence of SAIH as they typically decrease the sympathetic nervous system (SNS) tone (Flood et al., 2015). For example, morphine can suppress SNS tone leading to peripheral venous dilation and decreased venous return causing venous pooling, which ultimately results in reduced CO and hypotension (Flood et al., 2015). Additionally, some opioids such as morphine induce histamine release, which results in vasodilation and a subsequent drop in systemic blood pressure (Flood et al., 2015). When comparing the results from the non-obstetric group (two out of five) studies and the obstetric group (three out of six) studies supported the conclusion that ondansetron did not significantly attenuate SAIH (*See Table 2,3)*. Of these five studies, 4 used opioids in combination with the LA, which potentially increased the incidence of SAIH and, ultimately, their overall conclusions.

Another factor that may have influenced the incidence of SAIH reported in the studies reviewed was the dose of ondansetron administered before spinal anesthesia. In the non-obstetric group, both of the studies that found that ondansetron did not attenuate SAIH used 4mg of ondansetron, in the obstetric group, one third of the studies used ondansetron 4 mg and the other 2 used a max of 8 mg. Three of three of the non-obstetric groups who reported that ondansetron significantly attenuated the incidence of SAIH used more than 4 mg with a max of 12 mg of ondansetron (*See Table 2,3*). One third of the obstetric groups who found that

ondansetron significantly attenuated the incidence of SAIH used greater than 4mg of ondansetron; however, of the two who used 4 mg, neither used opioids in combination with the LA (*See Table 2,3*).

Study Limitations: This research study was not conducted without limitations. This literature review was restricted due to search strategy such as distinguishing differences between keywords, number of databases accessed, or the sources used, which might have had an impact on the quality and availability of the research. In addition, researcher and publication bias were limitations during this study.

Another limitation is the lack of familiarity with the Cochrane RoB tool. The lack of familiarity with this tool may have unintentionally led to selection for inclusion in this review of studies that had more RoB and exclusion of studies that had less RoB. The lack of uniformity amongst the different studies in this review concerning the amount of ondansetron and LA administered, and how hypotension was defined make it difficult to draw concrete conclusions based on the results reported.

Practical Implications: As the mixed results amongst the studies included have shown, it is unclear that the administration of prophylactic ondansetron before spinal anesthesia attenuates the incidence of SAIH in both obstetric and non-obstetric patients. Future studies must limit heterogeneity and include patients receiving emergency procedures. Exploration of different doses of ondansetron also needs further research to identify optimum ondansetron dosing.

Conclusion

The current study results showed mixed results that the prophylactic administration of ondansetron before spinal anesthesia was useful in the attenuation of SAIH in both obstetric and non-obstetric patients .

Tables

Table 1. Cochrane Risk of Bias (RoB) Tool.

	Selection Bias		**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Other Bias**
Author (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Prespecified
Iqbal et al., 2020	U	U	U	U	L	L	U
Bommala et al., 2019	L	L	L	U	L	L	U
Shah et al., 2019	L	L	L	U	L	L	U
Tatikonda et al.,2019	L	L	L	L	L	L	U
Karacaer et al., 2018	L	L	L	L	L	L	U
Oofuvong et al. 2018	U	L	L	L	L	L	U
Raghu et al., 2018	L	U	L	U	L	L	U
Baig et al., 2017	L	L	L	U	L	L	U
Potdar et al. 2017	U	L	H	H	L	L	U
Abbas et al., 2016	L	L	L	U	L	L	U
Jarineshin et al., 2016	U	U	U	L	L	L	U
Terkawi et al., 2015	L	L	L	L	L	L	U
Trabelsi et al., 2015	L	L	L	L	L	L	U
Marashi et al., 2014	L	U	L	L	L	L	U
Sahoo et al., 2014	L	L	L	L	H	L	U
Wang et al., 2014	L	U	L	U	L	L	U

Key: L=Low RoB, H=High RoB, U= unclear RoB

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Table 2. Incidence of Hypotension Non-Obstetric Patients. Key: LA= local anesthetic, SBP=systolic blood pressure, MAP= mean arterial pressure, % ↓ = from baseline

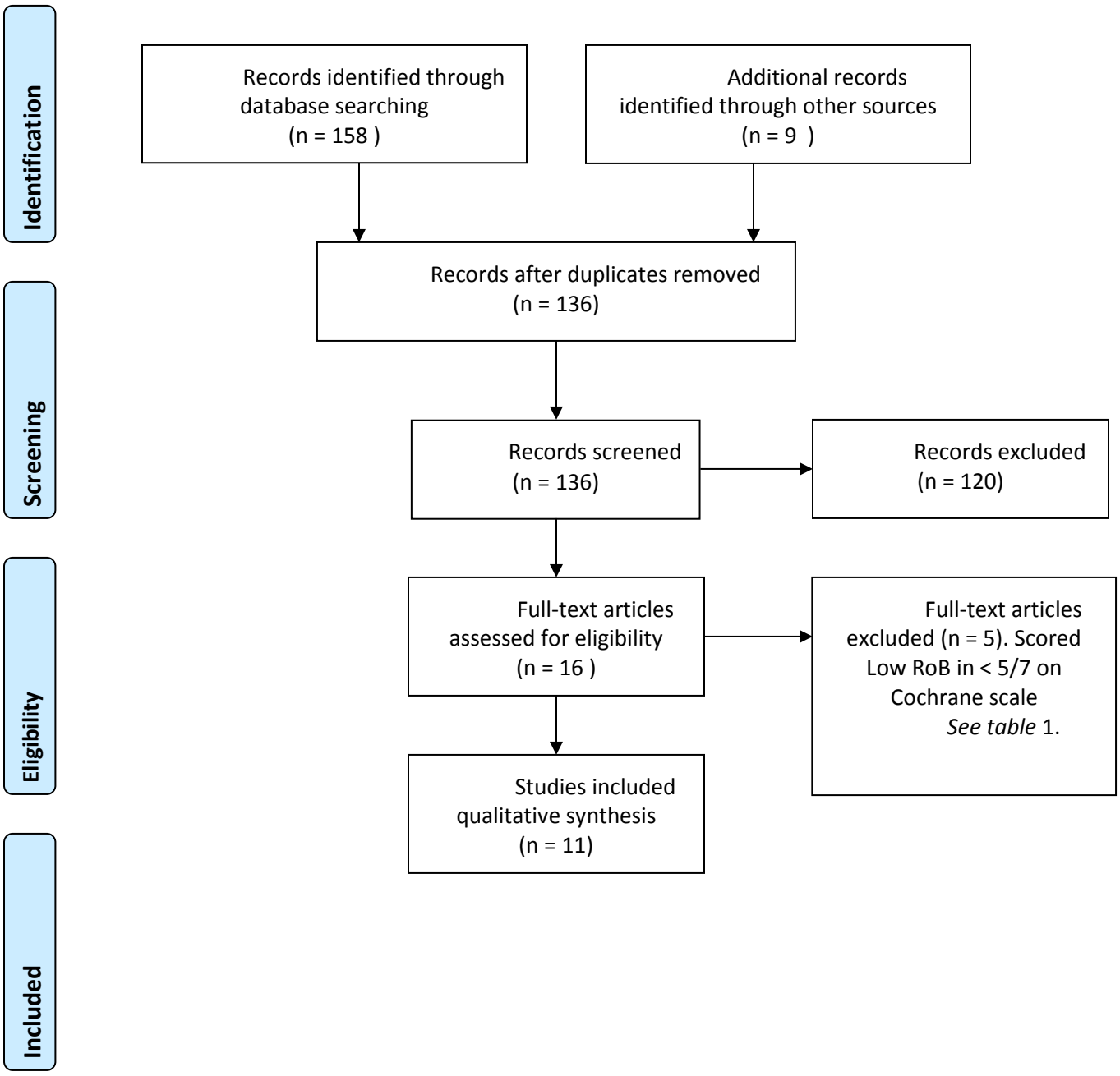
Author (year)	*Ondansetron (dose)*	*Placebo*	*LA (dose)*	*Definition of hypotension*	*Hypotension Ondansetron group*	*Hypotension placebo group*	*Significant P≤ 0.05 Y/N*
Bommala et al., 2019	n = 30 4mg	n = 30	Bupivacaine (15 mg) + 25 mcg fentanyl	30% ↓ SBP or < 90 mmHg	n = 7 (23%)	n = 14 (46.6%	P = 0.079 (N)
Shah et al., 2019	n = 50 8mg	n = 50	Bupivacaine (15 mg)	20% ↓ SBP or < 90mmHg	n = 23 (46%)	n = 36 (72%)	P = 0.026 (Y)
Tatikanda et al., 2019	n = 70 4mg	n = 70	Bupivacaine (15 mg)	20% ↓ MAP or < 80mmHg	n = 17 (24.3%)	n = 23 (32.9%)	P > 0.05 (N)
Baig et al., 2017	n = 53 (6mg)	n = 53	Bupivacaine (15 mg)	20% ↓ MAP or < 80mmHg	n = 4 (7.5%)	n = 15 (28.3%)	P = 0.005 (Y)
Marashi et al., 2014	n =140 6mg(n=70), 12mg(n=70)	n = 70	Bupivacaine (15 mg)	20% ↓ MAP or < 80mmHg	n = 0 (0%)	n = 12 (17%)	P = 0.04 (Y)

Table 3. Incidence of Hypotension in Obstetric Patients. Key: LA= local anesthetic, SBP=systolic blood pressure, MAP= mean arterial pressure, % ↓ = from baseline

Author (year)	*Ondansetron (dose)*	*Control (placebo)*	*LA (dose)*	*Definition of hypotension*	*Hypotension Ondansetron group*	*Hypotension placebo group*	*Significant if P≤ 0.05 Y/N*
Karacaer et al., 2018	n = 54 (8mg)	n = 54	Bupivacaine (10 mg) + 20 mcg fentanyl	20%↓ SBP	n = 47 (87%)	*n = 48* (89%)	P = 0.767 (N)
Oofuvong et al., 2018	n = 143 (.05mg/kg) = 71 (.1mg/kg) = 72 Max (8 mg)	n = 72	Bupivacaine (10 mg) + 200 mcg morphine	>30% ↓ MAP	.05mg n = 60 (84.5%) .1mg n = 53 (73.6%)	n = 59 (83%)	P = 0.23 (N)
Abbas et al., 2016	n = 50 (4mg)	n = 50	Bupivacaine (15 mg)	20%↓ SBP	n = 21 (42%)	n = 34 (72%)	P = 0.009 (Y)
Terkawi et al., 2015	n = 44 (8mg)	n = 42	Bupivacaine (15 mg) + 20 mcg fentanyl + 100 mcg morphine	SBP < 90mmHg	n = 26 (59.1%)	n = 25 (59.5%)	P = 1 (N)
Trabelsi et al., 2015	n = 40 (5mg)	n = 40	Bupivacaine (10 mg) + 2.5 mcg Sufentanil	≦20%↓ SBP or < 80mmHg	n = 15 (37.5%	n = 31 (77.5%)	P < 0.001 (Y)
Sahoo et al., 2012	n = 26 (4mg)	n = 26	Bupivacaine (10 mg)	SBP < 90 mmHg or DBP < 60 mmHg	n = 2 (8%)	n = 11 (42%)	P = 0.009 (Y)

Figures

Figure 1. **PRISMA 2009 Flow Diagram**



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. DOI:10.1371/journal.pmed1000097

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