Hypotension and bradycardia are common adverse effects following spinal anesthesia. Ondansetron has been studied in the attenuation of spinal anesthesia–induced hypotension (SIH) and bradycardia because of its antagonistic effect on the Bezold-Jarisch reflex. The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to determine the efficacy of intravenous (IV) ondansetron in reducing the incidence of SIH and bradycardia. Thirteen RCTs were included in this analysis, totaling 1,225 subjects. Hypotension and bradycardia were summarized using a risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was summarized using random-effects model for $I^2$ greater than 50%; otherwise, a fixed-effects model was performed.

Intravenous ondansetron reduced the incidence of hypotension in both the all-procedure analysis group (RR, 0.64; CI, 0.45-0.90) and cesarean delivery group (RR, 0.63; CI, 0.45-0.88). For bradycardia, IV ondansetron resulted in reduced risk (RR, 0.31; CI, 0.19-0.50). Findings of our meta-analysis suggest that IV ondansetron may mitigate the risks of SIH and bradycardia following spinal anesthesia.

**Keywords:** Bradycardia, ondansetron, spinal anesthesia–induced hypotension.

Hypotension and bradycardia are common sequelae to spinal anesthesia. Estimates of the incidence of spinal anesthesia–induced hypotension (SIH) are between 15% and 33% of cases.\textsuperscript{1,2} Prevalence varies because of individual patient history, comorbidities, and anesthetic technique. In addition, a universal definition of hypotension does not exist but is commonly described in relation to systolic pressure.\textsuperscript{2} The postulated mechanism for hypotension has been attributed to both venous and arterial vasodilation resulting from a local anesthetic–induced sympathetic blockade that can extend 2 to 6 dermatomes cephalad from the initial sensory level of the spinal anesthetic. Because the blood in the venous system is approximately 75% of the total blood volume, venodilation leads to venous pooling and reduction in venous return.\textsuperscript{3} Furthermore, the lack of a compensatory response to reflex tachycardia\textsuperscript{4} and vagal overactivity are contributing factors to the development of SIH.\textsuperscript{5}

Because most patients become tachycardic after induction of spinal anesthesia,\textsuperscript{6} the incidence of bradycardia is believed to result from an increase in parasympathetic tone, blockade of the cardioaccelerator nerve fibers, and decreased baroreceptor activity.\textsuperscript{2,7} Recently, the Bezold-Jarisch reflex (BJR) has been implicated as the most likely cause of bradycardia following spinal anesthesia.\textsuperscript{7} The BJR is a cardioinhibitory reflex producing bradycardia, hypotension, and cardiovascular collapse via nonmyelinated, type C fibers whose terminals lie in the chambers of the heart.\textsuperscript{7} Stimulation of peripheral serotonin receptors 5-hydroxytryptamine (5-HT3 type) elicits the BJR.\textsuperscript{8}

Two major reviews with meta-analysis identified prevention and treatment options for SIH.\textsuperscript{9,10} The goal of treatment is to restore preload, tighten peripheral vascular resistance, and improve cardiac output (CO). Multimodal treatment strategies include positioning, lower leg compression, loading and co-loading of crystalloids and colloids, and administration of pharmacologic vasopressors.\textsuperscript{9,10} Current evidence-based practice uses the prophylactic administration of $\alpha$- and $\beta$-adrenergic agonists, which have been shown to prevent and treat SIH.\textsuperscript{11} Recently, ondansetron has been studied to mitigate SIH and bradycardia.

Ondansetron, a 5-HT3 antagonist, is widely used for the prevention and treatment of postoperative nausea and vomiting. In light of its antagonistic effect on the 5-HT3 receptor, it may be an alternative agent in attenuating SIH and bradycardia. 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 hypotension and bradycardia associated with spinal anesthesia.
Methods

- **Search Strategy.** The current systematic review and meta-analysis of RCTs examining the effects of IV ondansetron in the attenuation of SIH and bradycardia was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.\(^\text{12,13}\) The electronic databases used in our literature search included MEDLINE (PubMed), Google Scholar, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and The Cochrane Review Database. The reference lists of retrieved studies were searched to identify additional potentially relevant publications. Only RCTs of prophylactic ondansetron (any dose) vs placebo or other interventions (other 5-HT3 antagonist, other pharmacologic intervention) administered before neuraxial blockade, in all types of surgery as long as spinal anesthesia was used as the primary anesthetic technique, were included in the review. Articles were retrieved using the following Medical Subject Headings (MeSH) terms and text words singularly and in combination: ondansetron, hypotension, spinal-induced hypotension, maternal hypotension, bradycardia, and spinal anesthesia. The date of the last computer search was August 11, 2015.

- **Study Selection.** Two authors (T.D.K, T.D.T.) assessed the titles and abstracts identified in the search using one common template. The inclusion criteria were full English text RCTs assessing the use of ondansetron for attenuation of SIH and bradycardia. The primary outcomes of this review were the incidence of hypotension and bradycardia (as defined by trial authors) when prophylactic ondansetron was given with spinal anesthesia.

- **Data Extraction/Risk of Bias.** The data from the included studies were extracted and tabulated independently. The validity of the studies was assessed and scored for methodological quality according to the Cochrane Handbook for Systematic Reviews.\(^\text{14}\) Risk of bias for included studies is presented in Figure 1. Differences of opinion were resolved by discussion or by adjudication of the third author (M.A.P.). The following information from each trial was obtained: number and age range of participants, ASA physical status classification of patients, definitions of hypotension and bradycardia, outcomes observed, rescue drugs used in the advent of hypotension (epinephrine, 5, 6, 10 mg; phenylephrine, 20, 50, 100 µg) and bradycardia (atropine, 0.1, 0.3, 0.5 mg; glycopyrrolate, 0.2 mg; ephedrine, 25 mg), types of local anesthetic, baricities and dosages, timing of fluid hydration (preloading and co-loading), type and amount of fluid loading, and the level of the sensory blockade. The dose of IV ondansetron and the timing of its administration were also recorded.

- **Summary of Measures and Statistical Analysis.** We used Review Manager (RevMan 5.3)\(^\text{15}\) for meta-analysis. We estimated the effects of ondansetron on the incidence of SIH and bradycardia by calculating pooled risk ratio (RR) with the 95% confidence interval (CI). For continuous variables, results were reported as a mean difference. The random-effects model for analysis was used, because we anticipated significant methodologic and clinical heterogeneity of data results. The criterion for statistical significance was \(P < .05\). Using the \(I^2\) statistic to assess variation between studies, we considered \(I^2\) values above 50% as evidence of heterogeneity.\(^\text{15}\) When the \(I^2\) was less than 50%, the data were pooled with a fixed-effects model. In extracted data containing significant heterogeneity, subgroup and sensitivity analyses were performed. For the primary outcome of hypotension, a subgroup analysis accounting for variations in the type of surgery and drug dosages was included in this review. We carried out sensitivity analysis of the primary outcome by excluding

![Figure 1. Risk of Bias Summary: Review Authors’ Judgments About Each Risk of Bias Item for Each Included Study](image)
trials that did not use a placebo. Publication bias was assessed using graphic funnel plot, and visual asymmetry was performed using the Egger test. PRISMA Guidelines for the reporting of systematic reviews were followed.12,13

Results
Initially, we reviewed 58 studies for eligibility by their titles and abstracts. We identified 17 potentially relevant trials and excluded 3 after a more thorough examination. We selected 14 RCTs for review; all were published between the years 2008 and 2015 in English-language, peer-reviewed journals. Of these, 1 study16 was excluded in the meta-analysis because we were unable to retrieve dichotomous results of the primary outcomes despite attempts to contact the primary authors for clarification. Finally, 13 RCTs met our inclusion criteria, and data of each RCT were included in our meta-analysis (Figure 2).

• Demographic Characteristics. The selected studies included 1,225 patients who received ondansetron vs placebo, other 5-HT3 antagonists, or other commonly used vasopressors before spinal anesthesia (Table). Demographic data were largely homogenous across the 9 studies17-25 of elective cesarean delivery and 4 trials26-29 reporting on a variety of surgical procedures in orthopedics, urology, and gynecology. Of these, 3 studies included older patients.27-29 All patients were ASA classification 1 or 2 except for 1 study.28 Patients in 9 trials17,18,20,22,24,26-29 received a preloading bolus of IV crystalloid solution, and subjects in 3 studies21,23,25 received IV colloid after IV cannulation. Only one of the included studies administered crystalloid using the coloading technique.19 Most studies evaluated ondansetron doses of 4 mg17-22,24,29 or 8 mg,18,21,23,25,27-29 whereas others reported results on 2 mg,18,21 6 mg,18,20 or 12 mg.20 Three studies22,24,29 compared IV ondansetron with granisetron, ramosetron, or ephedrine. All studies reported IV ondansetron administration 5 minutes before induction of spinal anesthesia.

The concentration of hyperbaric bupivacaine ranged between 0.5% and 0.75% with varying doses. Five studies added opioid in combination with the local anesthetic solution17,21,23,25,29. The level of sensory blockade before incision varied between studies depending on surgical procedures.

• Outcome Definitions. The 2 primary outcomes of interest were hypotension and bradycardia. Studies defined
<table>
<thead>
<tr>
<th>Source, year</th>
<th>N</th>
<th>Age (y) and ASA class</th>
<th>Type of surgery</th>
<th>Fluids and methods of hydration</th>
<th>Local anesthetic, concentration, dose, and additives</th>
<th>Position and lumbar site</th>
<th>Assessment of sensory level and height of sensory block</th>
<th>Definition and treatment (route) of hypotension</th>
<th>Definition and treatment (route) of bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owczuk et al.,27 2008</td>
<td>71</td>
<td>20-70 1-2</td>
<td>Non-OB</td>
<td>&lt; 200 mL NS Preloading</td>
<td>Bupivacaine 0.5% = 20 mg</td>
<td>Sitting to supine after SAB</td>
<td>Cold sensation using alcohol swab T8-T12</td>
<td>SBP &lt; 90 mm Hg</td>
<td>Ephedrine 10 mg (IV) Atropine 0.5 mg (IV)</td>
</tr>
<tr>
<td>Sahoo et al.,20 2012</td>
<td>52</td>
<td>20-40 1</td>
<td>Cesarean</td>
<td>20 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 10 mg</td>
<td>Sitting to supine with 15° tilt after SAB</td>
<td>Not reported</td>
<td>SBP &lt; 90 mm Hg</td>
<td>Phenylephrine 50 µg (IV) Atropine 0.3 mg (IV)</td>
</tr>
<tr>
<td>Rashad &amp; Farmawy,24 2013</td>
<td>60</td>
<td>20-40 1-2</td>
<td>Cesarean</td>
<td>20 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 10 mg</td>
<td>Sitting to supine with 15° left lateral tilt L3-4, L4-5</td>
<td>Short beveled 25-gauge needle, bilateral loss of pinprick at midclavicular line until sensory level is achieved</td>
<td>MAP ↓ 20%</td>
<td>Ephedrine 6 mg (IV) Atropine 0.5 mg (IV)</td>
</tr>
<tr>
<td>Marashi et al.,26 2014</td>
<td>210</td>
<td>20-50 1-2</td>
<td>Urologic, orthopedic, and gynecologic</td>
<td>5 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 15 mg</td>
<td>Lateral to supine after SAB</td>
<td>Pinprick caudal to cephalad direction T6</td>
<td>SBP &lt; 80 mm Hg or ↓ 20%</td>
<td>Ephedrine 10 mg (IV) Atropine 0.5 mg (IV)</td>
</tr>
<tr>
<td>Ortiz-Gomez et al.,21 2014</td>
<td>128</td>
<td>20-45 1</td>
<td>Cesarean</td>
<td>HES Preloading</td>
<td>Bupivacaine 0.5%; height (cm) × 0.06 mg Fentanyl 20 µg</td>
<td>Sitting to supine with 15° left tilt after SAB L3-4, L4-5</td>
<td>Cold sensation using alcohol swab T3</td>
<td>SBP ↓ 25%</td>
<td>Ephedrine 10 mg (IV) or phenylephrine 50 µg (IV) Atropine 0.1 mg/kg (IV)</td>
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<tr>
<td>Wang M et al.,18 2014</td>
<td>150</td>
<td>18-35 1-2</td>
<td>Cesarean</td>
<td>10 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 10 mg</td>
<td>Left tilt supine Not reported</td>
<td>Needle puncture method Not reported</td>
<td>SBP ↓ 20%</td>
<td>Phenylephrine 100 µg (IV) No treatment defined</td>
</tr>
<tr>
<td>Wang Q et al.,19 2014</td>
<td>66</td>
<td>18-35 1-2</td>
<td>Cesarean</td>
<td>10 mL/kg LRS Co-loading</td>
<td>Bupivacaine 0.5%: 10 mg</td>
<td>Left tilt supine Not reported</td>
<td>Needle puncture method Not reported</td>
<td>SBP ↓ 20%</td>
<td>Phenylephrine 100 µg (IV) Atropine 0.5 mg (IV)</td>
</tr>
<tr>
<td>Khalifa,22 2015</td>
<td>80</td>
<td>20-40 1-2</td>
<td>Cesarean</td>
<td>5 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 10 mg</td>
<td>Sitting to supine with 15° left tilt after SAB L3-4</td>
<td>Loss of fine pinprick sensation T5</td>
<td>MAP ↓ 20%</td>
<td>Phenylephrine 50 µg (IV) Atropine 0.5 mg (IV)</td>
</tr>
<tr>
<td>Study Authors</td>
<td>N</td>
<td>Range</td>
<td>Procedure</td>
<td>Fluid type</td>
<td>Local Anesthetic</td>
<td>Preloading</td>
<td>Sensation</td>
<td>SBP</td>
<td>Additional Measures</td>
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<tr>
<td>Marciniak et al.</td>
<td>72</td>
<td>18-40</td>
<td>Cesarean</td>
<td>10 mL/kg 6% HES Preloading</td>
<td>Bupivacaine 0.5% = 18-22 mg</td>
<td>Sitting to supine with 15° left tilt after SAB</td>
<td>Cold sensation T4</td>
<td>SBP &lt; 90 mm Hg or ↓ 20%</td>
<td>Ephedrine 10 mg (IV)</td>
</tr>
<tr>
<td>Owczuk et al.</td>
<td>53</td>
<td>&gt; 70</td>
<td>Non-OB</td>
<td>&lt; 200 mL NS Preload</td>
<td>Bupivacaine 0.5% = 12.5-15 mg</td>
<td>Sitting to supine after SAB</td>
<td>Cold sensation (alcohol swab) T10</td>
<td>SBP &lt; 90 mm Hg</td>
<td>Ephedrine 10 mg (IV)</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>117</td>
<td>20-75</td>
<td>Orthopedic</td>
<td>&lt; 200 mL Hartmann’s solution Preload</td>
<td>Bupivacaine 0.5%: 10-15 mg</td>
<td>Lateral to supine after SAB</td>
<td>Cold sensation T3</td>
<td>SBP &lt; 90 mm Hg or ↓ 20%</td>
<td>Ephedrine 5 mg (IV) or phenylephrine 20 µg (IV)</td>
</tr>
<tr>
<td>Terkawi et al.</td>
<td>86</td>
<td>Not reported</td>
<td>Cesarean</td>
<td>500 mL HES Preloading</td>
<td>Bupivacaine 0.75%: 15 mg</td>
<td>Sitting to supine with 15° left tilt after SAB</td>
<td>Cold sensation T3</td>
<td>SBP &lt; 90 mm Hg</td>
<td>Phenylephrine 100 µg (IV)</td>
</tr>
<tr>
<td>Trabelsi et al.</td>
<td>80</td>
<td>29-37</td>
<td>Cesarean</td>
<td>10 mL/kg LRS Preloading</td>
<td>Bupivacaine 0.5% = 10 mg</td>
<td>Sufentanil 2.5 µg</td>
<td>Loss of pinprick sensation (25-gauge hypodermic needle) T6</td>
<td>SBP &lt; 80 mm Hg or ↓ 20% IV fluid 100 mL</td>
<td>Ephedrine 10 mg (IV)</td>
</tr>
</tbody>
</table>

Table. Study Characteristics of Included Randomized Controlled Trials Reporting on Intravenous Ondansetron and Spinal Anesthesia–Induced Hypotension and Bradycardia

Abbreviations: Cesarean, cesarean delivery; HES, hydroxyethyl starch; IV, intravenous; LRS, lactated Ringer’s solution; MAP, mean arterial pressure; NS, normal saline; OB, obstetric; SAB, subarachnoid block; SBP, systolic blood pressure; ↓, decreased.

aPreloading, fluid administration before spinal induction; co-loading, rapid fluid administration.
bAll local anesthetics were hyperbaric solution.
cPatient position during and after induction of spinal anesthesia.
dLumbar intervertebral spaces, injection site of local anesthetic.
eTechniques used to assess sensory level.
fHighest level of sensory block.
gRoute of administration.
hypotension as a decrease in systolic blood pressure (SBP) by 75% to 80% of baseline.\textsuperscript{18,19,21} SBP less than 80 to 90 mm Hg. Two studies used mean arterial pressure to define hypotension.\textsuperscript{22,24} All patients (treatment and control groups) in whom hypotension developed were treated with ephedrine,\textsuperscript{17,24-28} phenylephrine,\textsuperscript{18-20,22,23} or a combination\textsuperscript{21,29} in varying doses.

Bradycardia was defined in beats per minute. In 3 studies, bradycardia was defined as less than 40 to 45/minute,\textsuperscript{21,28,29} in 5 studies as less than 50/minute,\textsuperscript{19,20,24,26,27} and in 2 studies as less than 60/minute.\textsuperscript{23,25} One study used 2 criteria to define bradycardia: either a 30% drop from baseline or a severe decline below 45/minute.\textsuperscript{17} Two studies did not specifically define bradycardia.\textsuperscript{18,22} Most patients were treated with varying doses of atropine,\textsuperscript{17,19-29} although fluids,\textsuperscript{17} ephedrine,\textsuperscript{17,24-28} and glycopyrrolate\textsuperscript{23} were occasionally used. One study did not discuss treatment for bradycardia despite reporting 3 subjects treated for bradycardia.\textsuperscript{18}

- **Spinal Anesthesia–Induced Hypotension.** Six RCTs\textsuperscript{17-20,22,26} favored the use of IV ondansetron administered before spinal anesthesia in attenuating SIH. Pooled analysis from the reviewed RCTs demonstrated that IV ondansetron reduced the incidence of SIH by a relative 36% (RR, 0.64; CI, 0.45-0.90). This analysis was affected by heterogeneity (I$^2$ = 73%). Results are presented in Figure 3.

Sensitivity analysis for SIH was performed after excluding 1 trial that did not use a placebo. In this trial, Shin and colleagues\textsuperscript{29} investigated the efficacy of ondansetron vs ramosetron. After exclusion of this study, meta-analysis of the remaining RCTs showed similar effects of ondansetron and SIH (RR, 0.58; CI, 0.41-0.82).

- **Bradycardia.** Eleven of the 13 RCTs\textsuperscript{17-20,22-28} involved subjects who experienced bradycardia in the placebo group, the treatment group or groups, or both. Two of the 13 studies\textsuperscript{17,26} reported statistically significant differences. Both Marashi et al\textsuperscript{26} (P = .02) and Trabelsi et al\textsuperscript{17} (P = .022) observed significant attenuation of spinal anesthesia-induced bradycardia in subjects pretreated with ondansetron. One of these studies\textsuperscript{26} evaluated 6 mg and 12-mg doses, and the other study\textsuperscript{17} assessed a 4-mg dose. Meta-analysis of the pooled data showed that treatment with ondansetron reduced the risk of bradycardia by a relative 69% (RR, 0.31; CI, 0.19-0.50). The heterogeneity was I$^2$ = 0%. Results are presented in Figure 4.

- **Subgroup Analysis and Investigation of Heterogeneity.** Based on a large amount of heterogeneity in the SIH data, a subgroup analysis was conducted. Studies involving cesarean delivery were analyzed separately from other operative procedures. In addition, different dosing was analyzed separately.

- **Maternal Hypotension.** Nine RCTs\textsuperscript{17-25} reported the incidence of hypotension during elective cesarean delivery (Figure 5). Of these, 5 studies\textsuperscript{17,20,22} showed a significant reduction in hypotension compared with placebo. Pooled analysis of the 9 RCTs showed that IV ondansetron attenuated maternal hypotension (RR, 0.63; CI, 0.45-0.88). Heterogeneity was lower compared with the all-procedure meta-analysis (I$^2$ = 68% vs. I$^2$ = 73%).

- **Nonobstetric Surgeries.** Four trial\textsuperscript{20-29} in the nonobstetric setting investigated the administration of IV ondansetron before spinal anesthesia. The pooled analysis revealed that pretreatment of IV ondansetron was not associated with a decrease in the incidence of SIH (RR, 0.45; CI, 0.12-1.66). The results showed a small effect size and large heterogeneity (I$^2$ = 83%).

- **Ondansetron by Dose.** Eight RCTs\textsuperscript{17,22,24,29} investigated the use of 4 mg of ondansetron compared with placebo. Of these, 1 study\textsuperscript{29} compared ondansetron with ramosetron. When combining data, regardless of the type of drugs in the control group, meta-analysis results showed reduction in SIH (RR, 0.57; CI, 0.35-0.93). However, pooled data from the 7 studies comparing ondansetron with placebo showed a higher reduction (22%) in the risks of hypotension compared with placebo (RR, 0.49; CI, 0.31-0.78). Heterogeneity across 7 studies was I$^2$ = 66%.

Intravenous ondansetron, 8 mg, was compared with placebo in 7 trials.\textsuperscript{18,21,23,25,27,29} Of these 7 RCTs, 1 study\textsuperscript{29} compared ondansetron with ramosetron. The pooled analysis revealed no difference between IV ondansetron in the incidence of SIH compared with placebo (RR, 0.86; CI, 0.69-1.06). The I$^2$ value of 23% indicated low heterogeneity.

Pooled data were analyzed from 3 studies evaluating 2-mg, 6-mg, or 12-mg dosing of ondansetron. Two RCTs\textsuperscript{18,21} reported 2 mg (RR, 0.99; CI, 0.70-1.39), 2 trials\textsuperscript{18,26} 6 mg (RR, 0.19; CI, 0.01-3.63), and 1 RCT\textsuperscript{26} reported 12 mg (RR, 0.04; CI, 0.00-0.66). Overall, there was no difference in the intervention group compared with control.

- **Risks of Bias.** The validity of each trial included in this review was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{14} Three studies\textsuperscript{22,24,26} had low risk of random sequence generation and 1 trial\textsuperscript{24} had low risk of allocation concealment. Blinding was adequate in all trials. All studies presented sample size calculation and a retention rate more than 80%. The Begg funnel plot of all studies included in this review is in Figure 6. The Egger test, performed using SAS version 9.4 (SAS Institute), showed visual asymmetry (Egger: bias = 1.99; CI, 0.50-2.70; P < .0001).

**Discussion**

This systematic review and meta-analysis of 13 RCTs shows that IV ondansetron given 5 minutes before the start of spinal anesthesia attenuates SIH. Furthermore, this
meta-analysis indicates that pretreatment with ondansetron strongly attenuates hypotension in subjects undergoing elective cesarean delivery. Additionally, the results of our meta-analysis indicate that IV ondansetron favors a reduction in the occurrence of bradycardia. In contrast to SIH, this review showed a significant reduction in the incidence of bradycardia with higher doses of ondansetron.

The cause of hypotension and bradycardia following...
induction of spinal anesthesia is multifactorial. One study proposed that the basis of SIH is reduction in systemic vascular resistance with concomitant inadequate increase in CO. During spinal anesthesia, neuraxial blockade reduces venous return. The reduction in preload triggers the BJR, which is mediated by the peripheral 5-HT3 type receptors. The BJR is an inhibitory cardiovascular response to noxious chemical substances and ventricular stretch sensed by the chemoreceptors and mechanoreceptors, which are primarily located in the wall of the left ventricle. The stimulation of the 5-HT3 type receptors increases parasympathetic activity and decreases sympathetic activity, resulting in the triad responses of bradycardia, vasodilation, and hypotension. In this review, ondansetron inhibits the BJR and attenuates SIH and bradycardia after spinal anesthesia.

Statistical heterogeneity among studies was present. Between-study heterogeneity might be attributed to the variable definitions of hypotension. To determine other sources of heterogeneity, we performed subgroup analyses that consisted of obstetric surgery, nonobstetric surgery, and different dosing of ondansetron. However, analyses of subgroups still indicated high heterogeneity. In our sensitivity analysis, we excluded 1 study that did not have a placebo group. However, the finding was virtually unchanged.

Other possible clinical factors for heterogeneity involved the timing and type of fluid used. A recent RCT regarding the timing of fluid administration has shown that co-loading (rapid administration of fluid during spinal anesthesia induction) is more efficient in preventing hypotension compared with preloading (administration of fluid before spinal anesthesia induction). In this current review, only 1 study used the co-loading approach. On the other hand, the use of colloids has been shown to be more effective than crystalloid. In this review, 3 studies used a type of colloid solution (Table).

The techniques used by practitioners to assess sensory blockade is another factor for clinical heterogeneity in our review. In a recent systematic review examining the multiple methods of assessing sensory blockade for cesarean delivery, the authors concluded that the use of cold or light touch is the common trend compared with pinprick. In our review, 6 RCTs used the cold sensation method to determine sensory block height, and 6 studies used pinprick. 6 trials did not indicate any form of assessment method.

Our review had some limitations. The number of participants in most of the RCTs included in our meta-analysis had small to medium effect size. Studies with a small sample size report larger effect size and may lead to reporting bias. The funnel plot shows some possibility of publication bias because of an asymmetric dispersion of effects. The inclusion of only English-language studies may suggest language bias and lead to a flawed conclusion. However, a systematic review of exclusion of other than English language found no evidence of systematic bias.

This review highlights areas where future studies are needed. Although our current analysis indicates statistical significance, we caution the extrapolation of results to clinical practice because of considerable heterogeneity between studies and small sample size. In our review, all participants were healthy and ASA classes 1 and 2 except for 2 studies that included older patients. In RCTs examining the obstetric patients, all participants were healthy, nonlaboring, singleton pregnancies scheduled for cesarean delivery. We recommend that future large-scale RCTs include patients with a history of pregnancy-induced hypertension, unplanned and emergency cesarean delivery, and those women who are in active labor. Elderly patients and patients with comorbidities have different implications from effects of hypotension and should be
investigated in future studies. The cost-effectiveness of IV ondansetron was not addressed by any of the studies included in the review. Overall, we recommend large-scale, double-blind trials with sufficient power to detect clinically relevant effects of IV ondansetron and SIH.

**Conclusion**

Results of our systematic review with meta-analysis support the hypothesis that ondansetron, administered intravenously 5 minutes before the placement of local anesthetic into the subarachnoid space, helps to attenuate SIH and bradycardia. Large, high-quality, randomized trials would limit heterogeneity among studies. Extending the RCTs to surgical procedures other than elective cesarean delivery and with various ondansetron dosing regimens will provide further validation of this potentially significant effect.

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