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Systematic Review

Ondansetron Reduces the Incidence of Hypotension after Spinal Anaesthesia: A Systematic Review and Meta-Analysis

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Abstract: Hypotension induced by spinal anaesthesia is a common clinical complication associated with multiple perioperative adverse events. We conducted a systemic review and meta-analysis to confirm whether ondansetron could alleviate hypotension following spinal anaesthesia. PubMed, Embase, Web of Science, and Cochrane Library were searched to identify eligible randomised controlled trials from their respective database inception dates to 30 September 2022. The primary outcome of the meta-analysis was the incidence of hypotension after spinal anaesthesia. The risk of bias in the included studies was evaluated using the revised Cochrane risk of bias tool for randomised trials (RoB 2.0). Grading of Recommendations, Assessment, Development, and Evaluation was applied to assess the level of certainty. A total of 25 studies were included in this research. The meta-analysis revealed that ondansetron significantly decreased the incidence of hypotension (RR = 0.65, 95% CI 0.53–0.80, $p < 0.01$, $I^2 = 64\%$) and bradycardia. In addition, patients treated with ondansetron had a reduced need for vasopressors administration. This study suggests that ondansetron may be recommended as a prophylaxis for hypotension and bradycardia following spinal anaesthesia; the level of evidence was moderate with a high level of heterogeneity.

Keywords: ondansetron; hypotension; meta-analysis; spinal anaesthesia

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1. Introduction

The recommended anaesthetic technique for various surgical procedures, including caesarean section, orthopaedic surgery, and lower abdominal general surgery, is spinal anaesthesia, also known as a subarachnoid block. However, hypotension caused by spinal anaesthesia is a common problem that plagues doctors and patients, occurring in approximately 80% of cases [1]. A reduction in blood pressure can cause a series of intraoperative adverse effects, such as dizziness, nausea and vomiting, regurgitation, and aspiration [2]. Therefore, it is important to investigate methods to reduce the incidence of hypotension following spinal anaesthesia that are economical, safe, and effective.

The mechanism of hypotension following spinal anaesthesia involves the reduction in vascular resistance caused by the sympathetic block and the activation of the Bezold–Jarisch reflex, leading to vasodilation and hypotension [3]. Peripheral serotonin receptors, 5-Hydroxytryptamine3 (5HT3), are required for the activation of the Bezold–Jarisch reflex [4]. In a rabbit model, a 5-HT3 receptor antagonist was reported to suppress bradycardia and hypotension by preventing the Bezold–Jarisch reflex [5]. Thus, numerous clinical trials have been performed to demonstrate the preventive effect of ondansetron on hypotension following spinal anaesthesia [6–8]. A meta-analysis published in 2016 argued that 5HT3 receptor antagonists effectively reduced the incidence of spinal anaesthesia-induced hypotension in patients undergoing caesarean sections but had no significant effect on a nonobstetric population [9]. A recent meta-analysis that was focused on the nonobstetric population treated with ondansetron contradicted that viewpoint [10]. However, in the aforementioned studies, the sample sizes were relatively small. Furthermore,

significant resources have been utilised annually on clinical trials on this topic worldwide [6,7,11–14]. Therefore, we conducted this systemic review and meta-analysis using trial sequential analysis (TSA) to investigate whether ondansetron prevents hypotension following spinal anaesthesia.

2. Methods

This systematic review and meta-analysis were performed and reported according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses. The registration number of the International Prospective Register of Systematic Reviews (PROSPERO) was CRD 42022353540.

2.1. Systematic Literature Search

The electronic databases of Web of Science, PubMed, Cochrane Library, and Embase were systematically searched. The retrieval date was from database establishment to 30 September 2022 without language limitations. The search terms included the following: "ondansetron", "5-HT3 receptor antagonists", "5-Hydroxytryptamine3", "spinal anaesthesia", "intrathecal anaesthesia", and "subarachnoid anaesthesia". Furthermore, the references of the eligible studies were also searched systematically.

2.2. Criteria for Selection

The eligibility requirements for inclusion were as follows: (1) Participants (P): patients receiving spinal anaesthesia. (2) Intervention (I): trials reporting ondansetron was administered intravenously. (3) Comparison (C): placebo. (4) Outcome (O): trials reporting the incidence of hypotension was one of the outcomes. (5) Study designs (S): randomised controlled trials (RCTs).

The following were the exclusion criteria for this research: (1) Combined with other types of anaesthesia, such as epidural and general anaesthesia. (2) Animal studies. (3) Incomplete studies, such as conference abstracts. (4) Ondansetron was administered by other means.

2.3. Extraction of Data and Outcomes

First, EndNote was used independently by two authors to exclude the duplicates. Second, they determined whether the trials met the conditions according to the title and abstract. Finally, the full texts of the screened studies were then carefully examined to determine whether they met all the inclusion criteria. Using data from the included studies, the two authors independently retrieved and cross-checked the following information: the author's name, year of publication, type of surgery, sample size, patients, blinding methods, details of spinal anaesthesia, dosage and timing of ondansetron, and the definition of hypotension. We emailed the corresponding authors of the research where some information was unavailable in the published articles. We sent another email enquiry if there was no response after more than a week.

The primary outcome of this study was the incidence of hypotension following spinal anaesthesia. (The definition of hypotension was based on that used in each clinical study) Secondary outcomes included the incidence of bradycardia, the use of vasopressor administration, and the dosage of ephedrine. If different doses or different types of ondansetron were studied, we combined the dichotomous variables for the meta-analysis. In the case of continuous variables, we analysed the data for different groups.

2.4. Evaluation of the Quality and the Risk of Bias

A revised Cochrane risk of bias tool for randomised trials (RoB 2.0) was used to assess the risk of bias in the included studies. The risk of bias table included bias from the process of randomisation, bias due to deviations from the expected interventions, bias from missing data, bias from the measurement of the outcome, and bias from the selection of the reported results. Each trial was assessed as either high risk, some concerns, or low risk.

The degree of confidence was assessed utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Accordingly, the level of certainty was categorised as very low, low, moderate, or high.

2.5. Statistical Analysis

The meta-analysis was performed using the Review Manager 5.3 (version 5.3, Copenhagen, Denmark) statistical software and Stata version 12.0 (Stata Corp LP, College Station, TX, USA). The pooled risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous outcomes were calculated. For continuous data, the mean differences (MD) and 95% CIs were evaluated. Statistical significance was considered to be achieved when the *p*-value was <0.05. The number needed to treat (NNT) was calculated for statistically significant outcomes. The heterogeneity in the trials was examined utilizing the I^2 statistic, wherein I^2 > 50% was defined as "highly heterogeneous". Clinical and methodological issues were shown to be the primary causes for high clinical heterogeneity. Consequently, a random-effects model was utilised even in studies with low I^2 values.

Subgroup analyses were performed according to the different dosages of ondansetron ($\leq$4 mg vs. >4 mg) and type of surgeries (caesarean section vs. non-caesarean section). For the trials that did not report the type of surgery and clearly did not belong to caesarean section (e.g., only included elderly patients, men, or specifically non-obstetric surgery), we analysed them in the non-caesarean section group. Funnel plots and Egger's test were employed to assess the publication bias. In addition, a sensitivity analysis was performed to test the stability of the primary outcome.

Using TSA software (version 0.9.5.10 beta), we performed a TSA method to control the risk of type I error caused by repeated testing. When the cumulative z-curve crosses the TSA monitoring boundary or enters the required information size line, no further study is required [15]. The risk of type 1 error was set as 5% with two-sided, and the power was 80%.

3. Results and Discussion

3.1. Search Results

According to the retrieval strategy, a total of 938 related studies were initially obtained from the databases. First, 245 duplicates were excluded, following which, 650 studies were removed once their titles and abstracts were reviewed. To determine whether the remaining 43 studies met the criteria for inclusion, their full texts were carefully analysed. Notably, 18 additional trials were omitted for the following reasons: conference abstracts (n = 3) [16–18] and no available outcomes (n = 15) [6,8,14,19–29]. Finally, a total of 25 trials that satisfied the eligibility requirements were selected for inclusion in the meta-analysis [2,11–13,30–50]. The schematic of the process of literature screening is depicted in Figure 1.

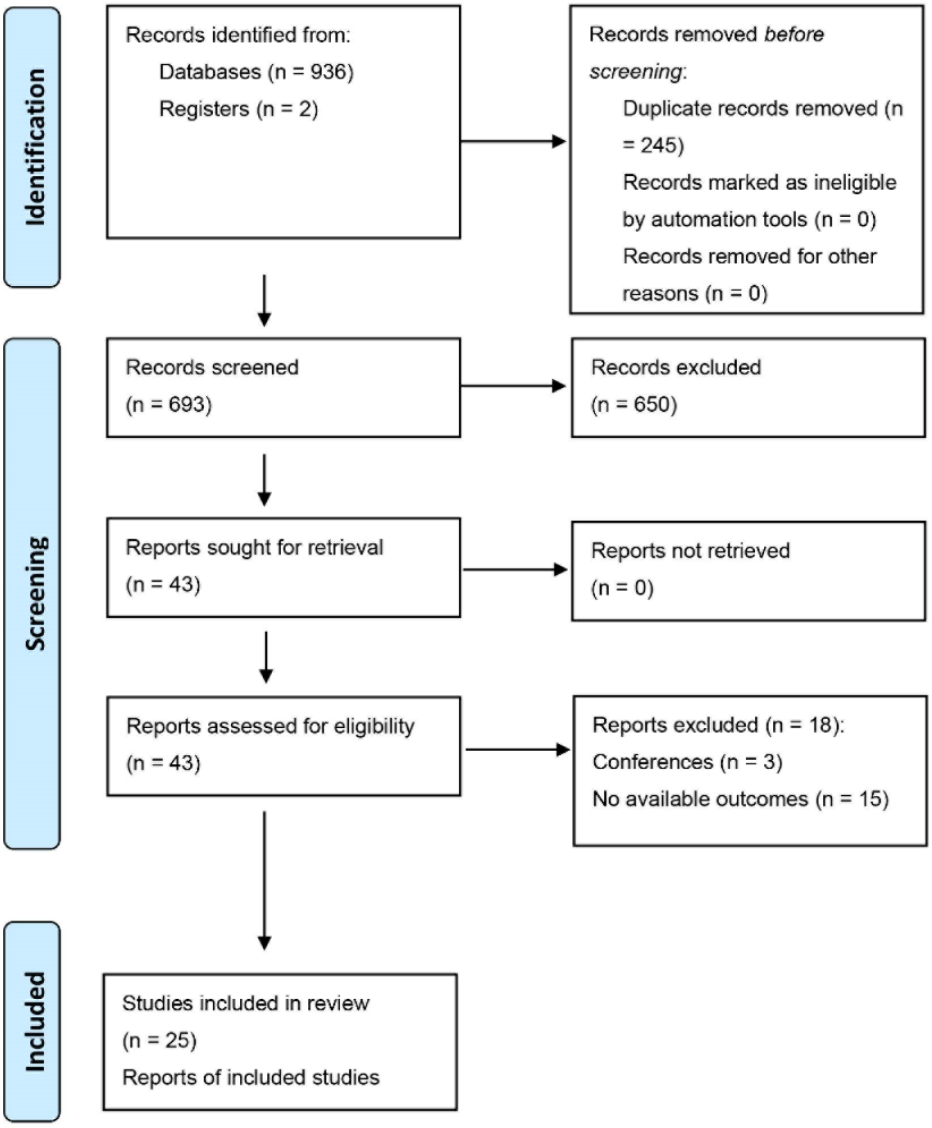

Figure 1. The literature retrieval and screening process according to the PRISMA guidelines.

3.2. Study Characteristics

In total, 25 RCTs comprising 2536 patients (1405 patients in the ondansetron group and 1131 patients in the control group) were analysed. The publication years for these studies were from 2005 to 2021, and the sizes of the samples were within a range of 40–254. The dosage of ondansetron ranged from 2 mg to 12 mg. One study was investigator-blinded [42], another study was patient-blinded [34], and the remaining studies were double-blinded. Only one trial did not clearly define hypotension following spinal anaesthesia [45]. Table 1 provides the detailed data on the specific features of the included studies.

Table 1. The details of the included studies.

Study	Sample Size	Type of Surgery	Patients	Blinded Method	Spinal Anaesthesia	Dosage of Ondansetron	Definition of Hypotension
Bhiwal 2021 [13]	O (4 mg): 48 O (8 mg): 50 Control: 50	Caesarean section	ASA: I–II Age range: 18–40	Double-blinded	Position: left lateral Local anaesthetic: 2 mL 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg or 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value.
Bommala 2019 [30]	O (4 mg): 30 Control: 30	Nonobstetric surgery	ASA: I–II Age range: 18–60	Double-blinded	Position: lateral decubitus Local anaesthetic: 3 mL 0.5% hyperbaric bupivacaine at L 3–4	Ondansetron 4 mg before spinal anaesthesia	Reduction in SBP by > 30% from the baseline value or SBP < 90 mmHg.
Haroon 2019 [31]	O (9 mg): 55 Control: 55	NR	ASA: I–III Age range: 51–81	Double-blinded	Position: Sitting Local anaesthetic: 17 mg 0.76% bupivacaine at L 4–5	Ondansetron 9 mg before spinal anaesthesia	Reduction in SBP by > 21% from the baseline value or SBP < 91 mmHg.
Kelsaka 2006 [32]	O (8 mg): 25 Control: 25	Orthopaedic surgery	ASA: I–II Age range: 20–60	Double-blinded	Position: lateral Local anaesthetic: 2.5 mL 0.5% hyperbaric bupivacaine at L 3–4	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value.
Marashi 2014 [2]	O (6 mg):70 O (12 mg):70 Control: 70	Urologic, orthopaedic or gynaecologic surgeries	ASA: I–II Age range: 20–50	Double-blinded	Position: lateral Local anaesthetic: 15 mg of 0.5% hypertonic bupivacaine at L 3–4 or L 4–5	Ondansetron 6 mg or 12 mg before spinal anaesthesia	Reduction in MAP by > 20% from the baseline value or MAP < 80 mm Hg.
Rashad 2013 [42]	O (4 mg):20 Control: 20	Caesarean section	ASA: I–II Age range: 20–40	Investigator-blinded	Position: Sitting Local anaesthetic: 2 mL 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg before spinal anaesthesia	Reduction in MAP by > 20% from the baseline value.
Marciniak 2015 [33]	O (8 mg): 36 Control: 34	Caesarean section	ASA: I–II Age range: NR	Double-blinded	Position: Sitting Local anaesthetic: 0.5% hypertonic bupivacaine at L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value or SBP < 90 mmHg.
Mendonça 2021 [12]	O (8 mg): 72 Control: 72	Nonobstetric surgery	ASA: I–II Age range: ≥18	Double-blinded	Position: Sitting Local anaesthetic: hyperbaric bupivacaine (15 mg or more)	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value or SBP < 90 mmHg.
Mohamed 2021 [11]	O (10 mg): 38 Control: 38	Caesarean section	ASA: I–II Age range: NR	Double-blinded	Position: Sitting Local anaesthetic: 12.5 mL 0.5% isobaric bupivacaine. at L 3–4	Ondansetron 10 mg before spinal anaesthesia	Reduction in MAP by > 20% from the baseline value.
Mohamed 2018 [34]	O (4 mg): 45 Control: 45	NR	ASA: I Age range: 18–45	Patient-blinded	Position: Sitting Local anaesthetic: 2.5–3 mL 0.5% hyperbaric bupivacaine at L 3–4	Ondansetron 4 mg before spinal anaesthesia	Reduction in MAP by > 20% from the baseline value or MAP < 70 mm Hg.
Mohammadzadeh 2021 [35]	O (4 mg): 127 Control: 127	Caesarean section	ASA: II Age range: 18–40	Double-blinded	Position: Sitting Local anaesthetic: 12.5 mg isobar bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg after spinal anaesthesia	Reduction in BP by > 20% from the baseline value or BP < 100 mm Hg.

Table 1. *Cont.*

Study	Sample Size	Type of Surgery	Patients	Blinded Method	Spinal Anaesthesia	Dosage of Ondansetron	Definition of Hypotension
Nallam 2017 [36]	O (8 mg): 40 Control: 40	Caesarean section	ASA: I–II Age range: 22–32	Double-blinded	Position: Sitting Local anaesthetic: 12.5 mg 0.5% hyperbaric bupivacaine L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	Reduction in BP by > 20% from the baseline value or MAP below 60 mmHg.
Ortiz-Gómez 2014 [37]	O (2 mg):32 O (4 mg):32 O (8 mg):32 Control: 32	Caesarean section	ASA: I Age range: 20–45	Double-blinded	Position: Sitting Local anaesthetic: 0.5% hyperbaric bupivacaine L 3–4 or L 4–5	Ondansetron (2, 4 or 8 mg) before spinal anaesthesia	Reduction in SBP by > 25% from the baseline value.
Owczuk 2008 [38]	O (8 mg): 36 Control: 35	NR	ASA: I–II Age range: 20–70	Double-blinded	Position: Sitting Local anaesthetic: 4 mL 0.5% hyperbaric bupivacaine L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	SBP < 90 mmHg.
Owczuk 2015 [39]	O (8 mg): 26 Control: 27	NR	ASA: I–III Age range: >70	Double-blinded	Position: Sitting Local anaesthetic: 2.5 to 3 mL 0.5% hyperbaric bupivacaine at L 2–3 or L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value or SBP < 90 mmHg.
Pirat 2005 [40]	O (4 mg): 50 Control: 50	Inguinal hernia, cord hydrocele, and pilonidal sinus	ASA: NR Age range: NR	Double-blinded	Position: Sitting Local anaesthetic: 12.5 mg or 15 mg 0.5% hyperbaric bupivacaine at L 2–3 or L 3–4	Ondansetron 4 mg before spinal anaesthesia	Reduction in SBP by > 15% from the baseline value.
Ramon 2017 [41]	O (8 mg): 65 Control: 65	Caesarean section	ASA: I Age range: 20–45	Double-blinded	Position: Sitting Local anaesthetic: 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 25% from the baseline value.
Safavi 2014 [43]	O (8 mg): 40 Control: 40	Orthopaedic surgery	ASA: I–II Age range: 16–65	Double-blinded	Position: Sitting Local anaesthetic: 0.5% hyperbaric bupivacaine at L 3–4	Ondansetron 8 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value.
Sahoo 2012 [44]	O (4 mg): 26 Control: 26	Caesarean section	ASA: I Age range: 20–40	Double-blinded	Position: Sitting Local anaesthetic: 2 mL 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg before spinal anaesthesia	SBP < 90 mmHg or DBP < 60 mmHg.
Shakya 2010 [45]	O (4 mg): 40 Control: 40	General and gynaecological surgery	ASA: I Age range: NR	Double-blinded	Position: NR Local anaesthetic: 3 mL 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg after spinal anaesthesia	NR.
Tatikonda 2019 [46]	O (4 mg): 70 Control: 70	Orthopaedic, gynaecological, and general surgical procedures	ASA: I–II Age range: 20–60	Double-blinded	Position: Sitting Local anaesthetic: 3 mL 0.5% hyperbaric bupivacaine at L 3–4 or L 4–5	Ondansetron 4 mg before spinal anaesthesia	Reduction in MAP by > 20% from the baseline value.

Table 1. *Cont.*

Study	Sample Size	Type of Surgery	Patients	Blinded Method	Spinal Anaesthesia	Dosage of Ondansetron	Definition of Hypotension
Terkawi 2015 [47]	O (8 mg): 44 Control: 42	Caesarean section	ASA: I Age range: NR	Double-blinded	Position: recumbent Local anaesthetic: 15 mg 0.75% bupivacaine at L 3–4 or L 4–5	Ondansetron 8 mg before spinal anaesthesia	SBP < 90 mmHg.
Trabelsi 2015 [48]	O (4 mg): 40 Control: 40	Caesarean section	ASA: NR Age range: NR	Double-blinded	Position: sitting Local anaesthetic: 2 mL hyperbaric bupivacaine at L 2–3 or L 3–4	Ondansetron 4 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value or SBP < 80 mmHg.
Wang M 2014 [49]	O (2 mg): 29 O (4 mg): 30 O (6 mg): 29 O (8 mg): 30 Control: 30	Caesarean section	ASA: I–II Age range: 18–35	Double-blinded	Position: NR Local anaesthetic: 2 mL 0.5% hyperbaric bupivacaine	Ondansetron (2, 4, 6, or 8 mg) before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value.
Wang Q 2014 [50]	O (4 mg): 33 Control: 32	Caesarean section	ASA: I–II Age range: 18–35	Double-blinded	Position: NR Local anaesthetic: 2 mL 0.5% hyperbaric bupivacaine	Ondansetron 4 mg before spinal anaesthesia	Reduction in SBP by > 20% from the baseline value.

Abbreviation: O, ondansetron; NR, not reported; SBP, systolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; DBP, diastolic blood pressure.

3.3. Assessment of Bias

Eight trials had a high risk of bias in the "randomisation process", while five trials had some concerns of bias in the "measurement of the outcome". Only six trials had a pre-registered protocol, and the "selection of the reported results" was graded as low risk. Figure 2 presents the overall findings of the bias evaluation.

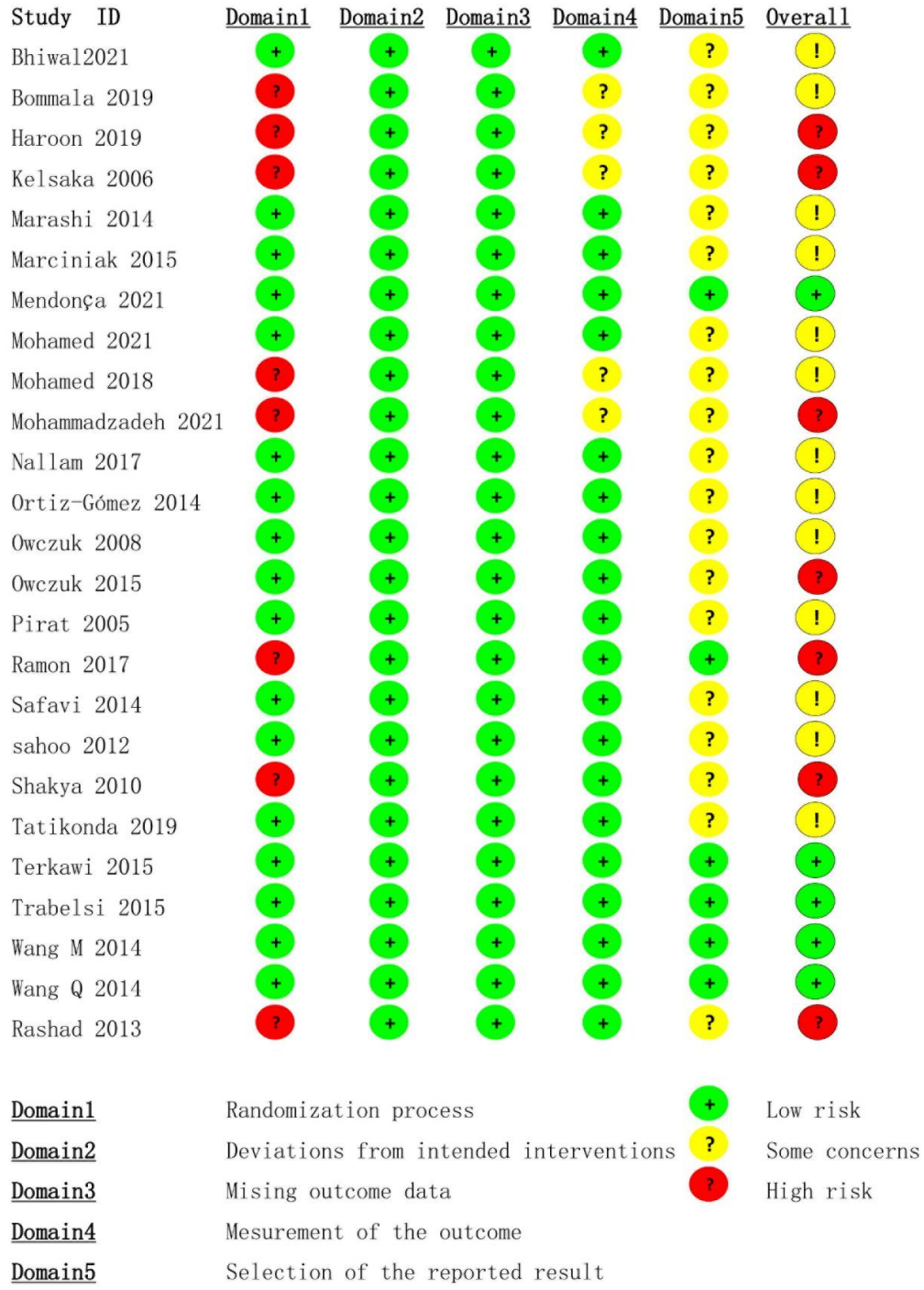

Figure 2. Summary of the risk of bias results for the included studies [2,11–13,30–50].

3.4. The Incidence of Hypotension

All the included trials reported the incidence of hypotension. The meta-analysis demonstrated that ondansetron reduces the occurrence of hypotension as compared to the control group, with high heterogeneity (RR = 0.65, 95% CI 0.53–0.80, $p < 0.01$, $I^2 = 64\%$,

Figure 3). The NNT was 7.5. Subgroup analyses were performed to explore the sources of heterogeneity according to different dosages of ondansetron and surgical modalities. However, heterogeneity was not significantly reduced (Supplementary Figures S1 and S2).

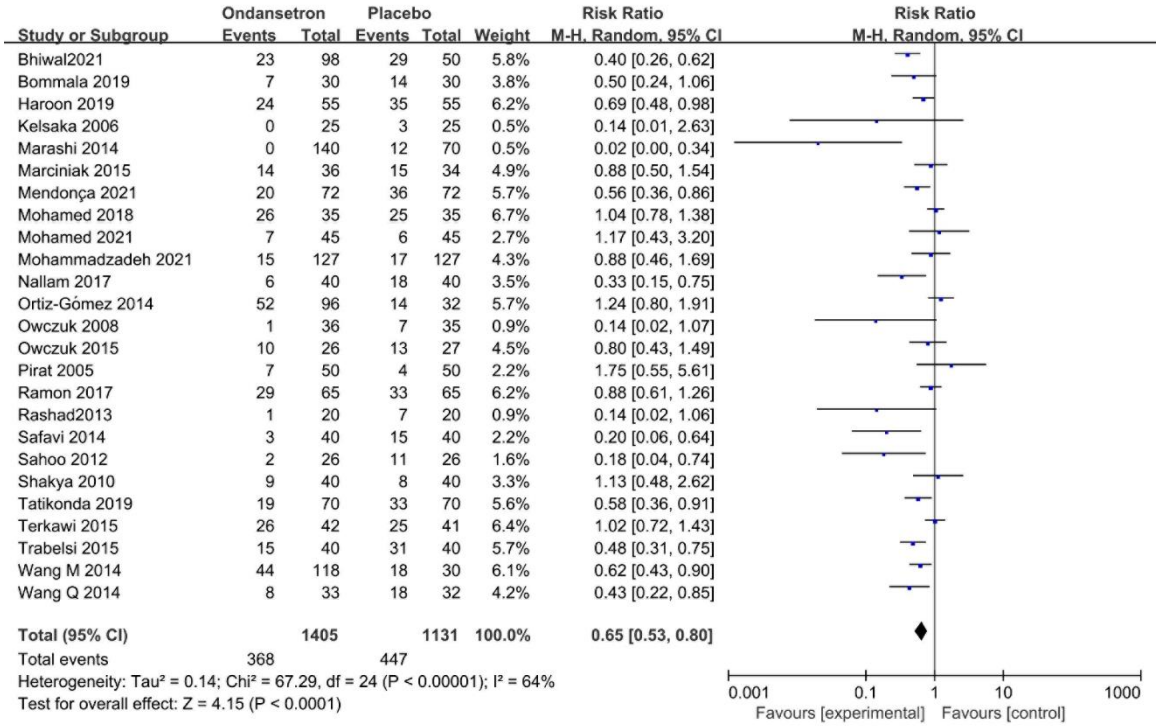

Figure 3. Forest plot of the pooled analysis showing the incidence of hypotension [2,11–13,30–50].

3.5. The Incidence of Bradycardia

Eighteen trials recorded the incidence of bradycardia. The forest plot demonstrated that patients treated with ondansetron had a significantly lower occurrence of bradycardia, with low heterogeneity (RR = 0.56, 95% CI 0.38–0.83, $p < 0.01$, $I^2 = 8\%$, Figure 4). The NNT was 16.7.

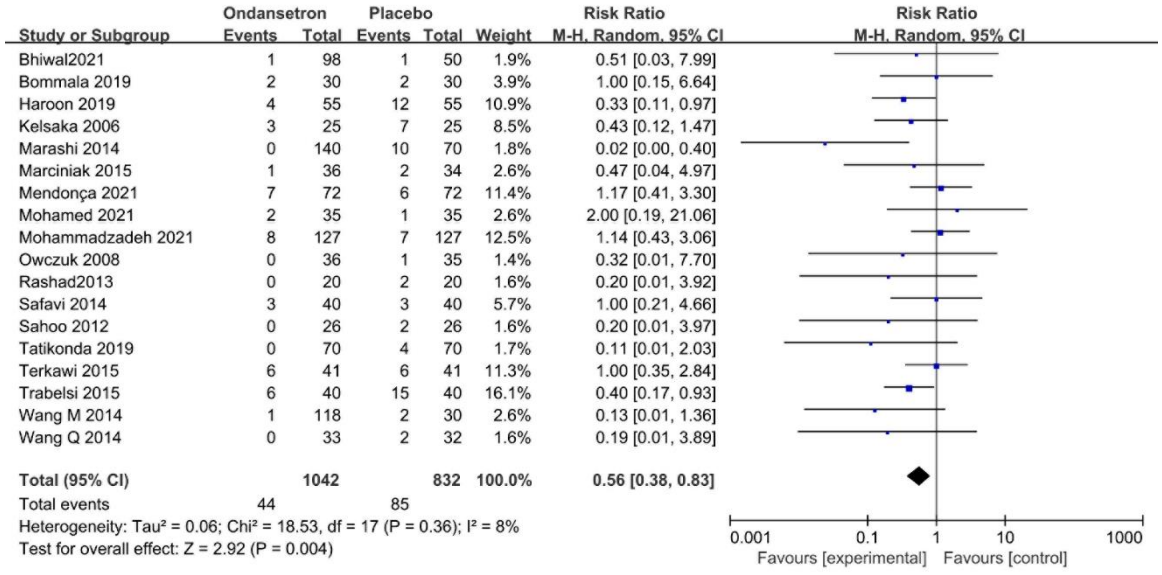

Figure 4. Forest plot of the pooled analysis showing the incidence of bradycardia [2,11–13,30–33,35,38,42–44,46–50].

3.6. Rescue of Vasopressor Administration

Fifteen trials assessed the number of patients who required vasopressor administration. The forest plot indicated that ondansetron significantly reduced the number of patients who required vasopressor administration following spinal anaesthesia, with low heterogeneity (RR = 0.50, 95% CI 0.38–0.67, $p < 0.01$, $I^2 = 38\%$, Figure 5).

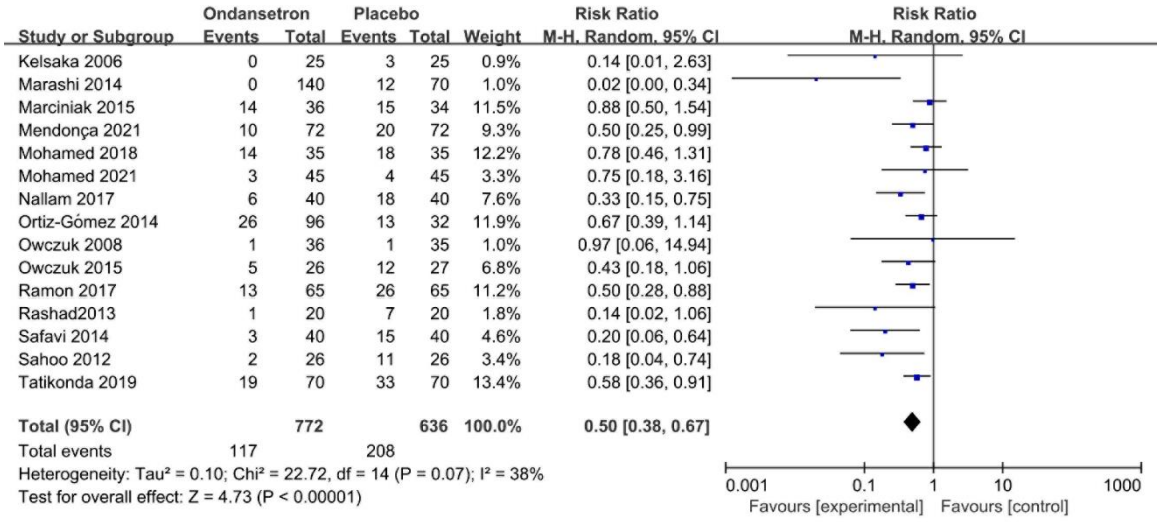

Figure 5. Forest plot of the pooled analysis showing the number of patients who required vasopressor [2,11,12,32–34,36–39,41–44,46].

Four trials reported the dosage of administered ephedrine following spinal anaesthesia. The result revealed that patients in the ondansetron group had a lower dose of administered ephedrine, with high heterogeneity (MD = −2.81 mg, 95% CI [−4.72, −0.89], $p < 0.05$, $I^2 = 77\%$, Figure 6).

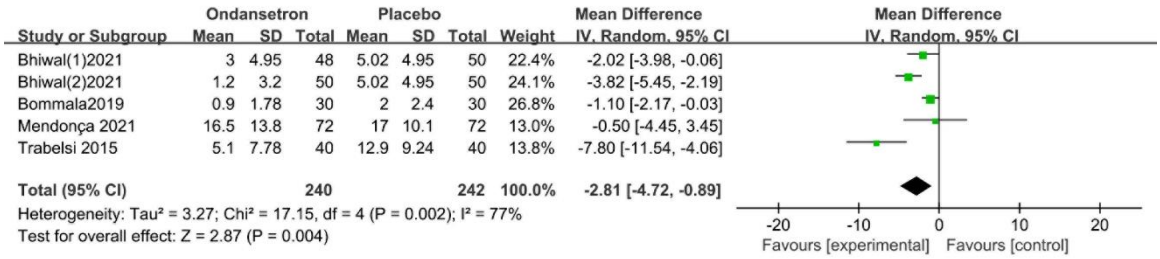

Figure 6. Forest plot of the pooled analysis showing the dose of administered ephedrine [12,13,30,48].

3.7. Publication Bias and Sensitivity Analysis

The funnel plot of the incidence of hypotension revealed a basically symmetric distribution, and the Egger's test *p*-value was 0.554 (>0.05), suggesting there was no obvious publication bias (Figure 7). Sensitivity analysis was performed on the incidence of hypotension with unchanged effect estimates, indicating the robustness of the pooled result (Supplementary Figure S3).

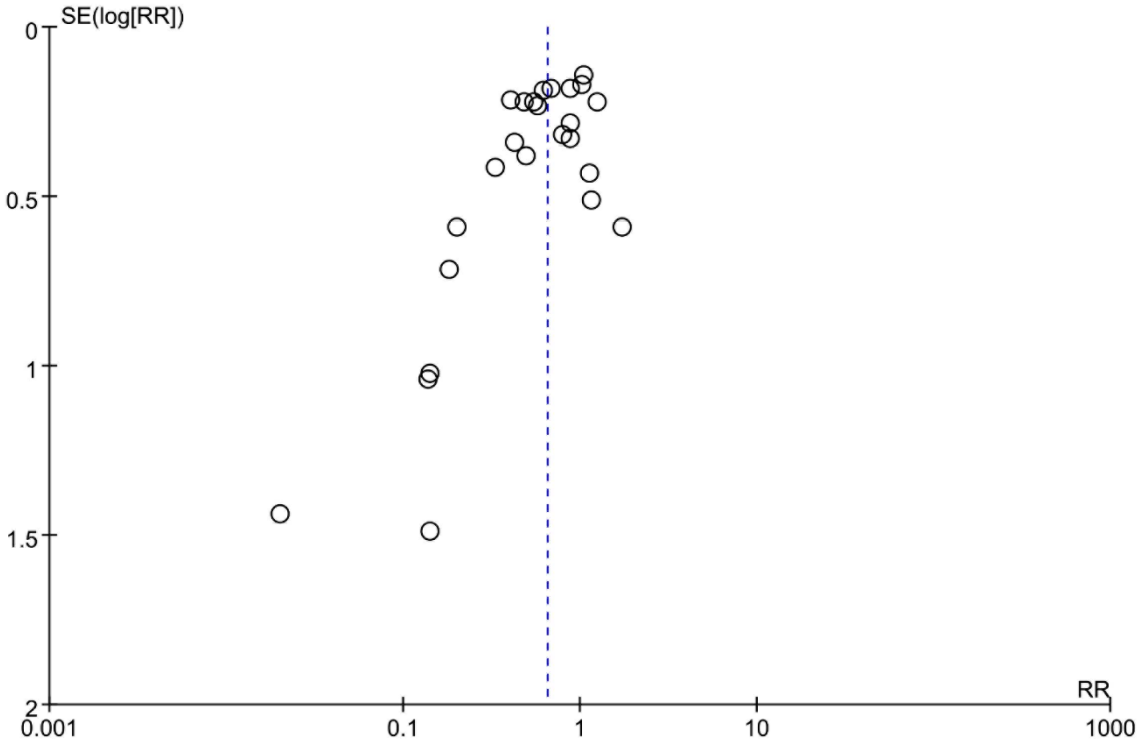

Figure 7. The funnel plot of the incidence of hypotension.

3.8. Trial Sequential Analysis

The TSA result for hypotension incidence showed that the cumulative z-curve had reached both the traditional and TSA boundaries, and that further studies were not required to confirm this evidence (Figure 8).

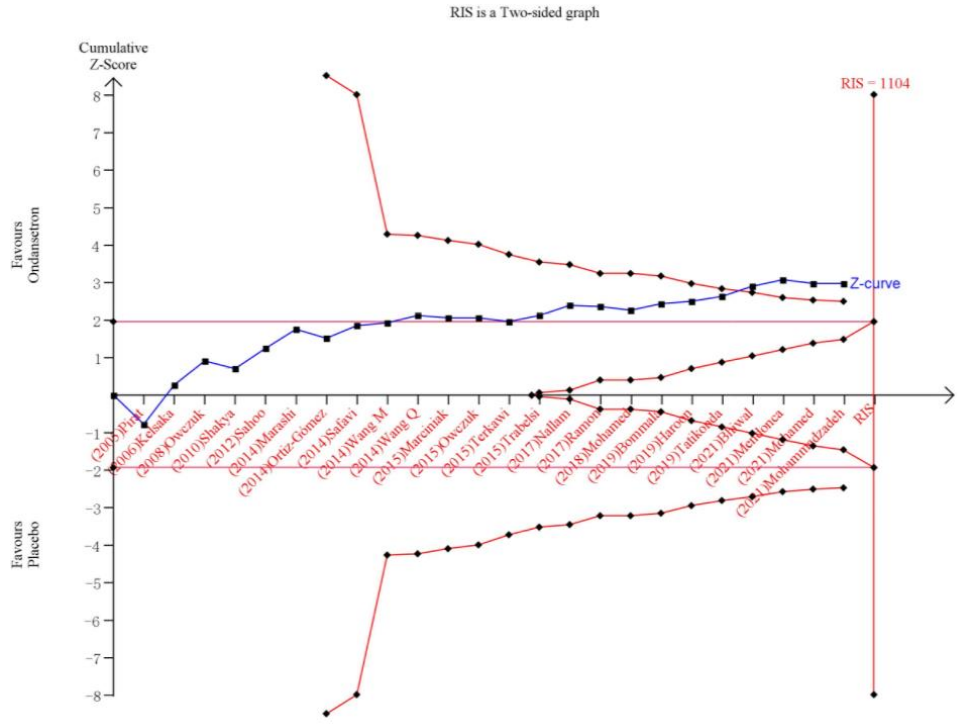

Figure 8. The trial sequential analysis result for the incidence of hypotension.

3.9. Grade Evaluation

All the studies considered in this review used the randomised trial "study design" type. The I^2 values of some reports were high to a relative extent, while the "inconsistency" was graded as serious. No obvious publication bias was evaluated among the evidence. The overall GRADE results are summarised in Table 2.

Table 2. The overall results of the GRADE evaluation.

Outcome	MD/RR (95% CI)	Level of Certainty	Reasons
Incidence of hypotension	0.65 (0.53, 0.80)	⊕⊕⊕○ MODERATE	Inconsistency was "serious".
Incidence of bradycardia	0.56 (0.38, 0.83)	⊕⊕⊕⊕ HIGH	None.
Rescue of vasopressor administration	0.50 (0.38, 0.67)	⊕⊕⊕⊕ HIGH	None.
Administration of ephedrine	−2.81 (−4.72, −0.89)	⊕⊕⊕○ MODERATE	Inconsistency was "serious".

MD, mean difference; RR, risk ratio; ⊕, not serious; ○, serious.

3.10. Discussion

This systematic analysis and meta-analysis revealed that the prophylactic administration of ondansetron may significantly reduce the risks of hypotension (moderate-quality evidence), bradycardia (high-quality evidence), and the need for vasopressor administration rescue (high-quality evidence) in patients undergoing spinal anaesthesia. According to the TSA, there was sufficient evidence to support the fact that ondansetron prevents hypotension after spinal anaesthesia.

In recent years, studies have been conducted on different treatments for hypotension following spinal anaesthesia, such as fluid therapy and vasopressors [51,52]. However, the activation of the Bezold–Jarisch reflex is one of the important mechanisms of hypotension after spinal anaesthesia. Numerous studies have focused on preventing hypotension by attenuating the Bezold–Jarisch reflex with 5-HT3 receptor antagonists [2,11–13,30,39,46,47,49,53]. Ondansetron was demonstrated to be effective in preventing hypotension in previous meta-analyses [9,10,54,55]. However, the promotion of its clinical application was constrained by the specific type of surgery and the limited sample size. Our meta-analysis of 25 RCTs revealed that ondansetron can significantly reduce the risks of hypotension (NNT 7.5) and bradycardia (NNT 16.7), which is consistent with previous studies. Sensitivity analysis results supported the robustness of the combined results of this study.

Notably, the TSA findings indicated that the information size for supporting the role ondansetron plays was sufficient, meaning that there is no need to spend more resources on clinical trials to investigate its effectiveness. In addition, we evaluated the preventive effect of ondansetron on hypotension by subgroup analysis at different doses (low-dose vs. high-dose) and different surgical types (caesarean section vs. non-caesarean section). The results of the subgroup analyses were consistent with the overall result. However, we did not conduct a meta-analysis for other types of 5-HT3 receptor antagonists due to the insufficient trials. Therefore, to extend this finding to other types of 5-HT3 receptor antagonists, additional high-quality RCTs are required.

In addition, we found that patients treated with ondansetron had a lower need for vasopressor administration and a lower dosage of administered ephedrine, which were consistent with previous studies [9,12]. This was mainly attributed to the lower incidence of hypotension. However, we did not conduct a meta-analysis for the dosage of phenylephrine due to the low number of trials. Recent studies have indicated that phenylephrine has become the first-line treatment because of a more favourable effect on neonatal pH compared with ephedrine [56].

There was significant clinical heterogeneity, which may be related to the different patient populations (age, disease, obstetric, sex, etc.), types of surgery, different dosages

of ondansetron, type of spinal anaesthesia and drug, definition of hypotension, and the technique to measure blood pressure. Therefore, a random-effects model was adopted in this meta-analysis. Due to the high level of heterogeneity, the quality of evidence for the primary outcome was moderate.

This study had some limitations. First, some included studies did not clearly report the method of randomisation, leading to a decline in study quality. Second, meta-analyses for other types of 5-HT3 receptor antagonists were not conducted due to insufficient data. Third, some included studies did not report the type of surgery, which could lead to potential bias. Finally, definitions of hypotension and bradycardia varied across studies, causing potential bias.

4. Conclusions

This study provided evidence that ondansetron may serve as a clinical option for the prevention of hypotension and bradycardia following spinal anaesthesia. Further research is needed to determine whether the effect is similar for other types of 5-HT3 receptor antagonists.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph15121588/s1, Figure S1: Forest plot of the pooled analysis showing the subgroup analysis for the incidence of hypotension according to different dosage of ondansetron, Figure S2: Forest plot of the pooled analysis showing the subgroup analysis for the incidence of hypotension according to different type of surgical modalities, Figure S3: Sensitivity analysis for the incidence of hypotension.

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References

1. Pereira, I.D.F.; Grando, M.M.; Vianna, P.T.; Braz, J.R.; Castiglia, Y.M.; Vane, L.A.; Módolo, N.S.P., Jr.; do Nascimento, P., Jr.; Amorim, R.B.; Rolim Rodrigues, G., Jr.; et al. Retrospective analysis of risk factors and predictors of intraoperative complications in neuraxial blocks at Faculdade de Medicina de Botucatu-UNESP. *Rev. Bras. Anestesiol.* **2011**, *61*, 844–866. [CrossRef] [PubMed]
2. Marashi, S.M.; Soltani-Omid, S.; Soltani Mohammadi, S.; Aghajani, Y.; Movafegh, A. Comparing Two Different Doses of Intravenous Ondansetron with Placebo on Attenuation of Spinal-induced Hypotension and Shivering. *Anesthesiol. Pain Med.* **2014**, *4*, e12055. [CrossRef] [PubMed]
3. Kinsella, S.M.; Tuckey, J.P. Perioperative bradycardia and asystole: Relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br. J. Anaesth.* **2001**, *86*, 859–868. [CrossRef] [PubMed]
4. Martinek, R.M. Witnessed asystole during spinal anesthesia treated with atropine and ondansetron: A case report. *Can. J. Anaesth. J. Can. D'anesthesie* **2004**, *51*, 226–230. [CrossRef] [PubMed]
5. White, C.M.; Chow, M.S.; Fan, C.; Kluger, J.; Bazunga, M. Efficacy of intravenous granisetron in suppressing the bradycardia and hypotension associated with a rabbit model of the Bezold-Jarisch reflex. *J. Clin. Pharmacol.* **1998**, *38*, 172–177. [CrossRef]
6. Kannan, M.H.; Heggeri, V.M.; Kumaran, R.M. Ondansetron Attenuates Hypotension Due to Subarachnoid Block-A Randomised Double Blind, Placebo-Controlled Study. *J. Res. Med. Dent. Sci.* **2022**, *10*, 414–420.
7. Xiao, F.; Wei, C.; Chang, X.; Zhang, Y.; Xue, L.; Shen, H.; Ngan, K.; Warwick, D.; Chen, X. A Prospective, Randomized, Double-Blinded Study of the Effect of Intravenous Ondansetron on the Effective Dose in 50% of Subjects of Prophylactic Phenylephrine Infusions for Preventing Spinal Anesthesia-Induced Hypotension During Cesarean Delivery. *Anesth. Analg.* **2020**, *131*, 564–569. [CrossRef]

8. Attri, A.; Sharma, N.; Singh, M.R.; Bansal, K.; Singh, S. Effect of intravenous ondansetron on maternal hemodynamics during elective caesarean section under subarachnoid block. *J. Obstet. Anaesth. Crit. Care* **2019**, *9*, 94.
9. Heesen, M.; Klimek, M.; Hoeks, S.E.; Rossaint, R. Prevention of Spinal Anesthesia-Induced Hypotension During Cesarean Delivery by 5-Hydroxytryptamine-3 Receptor Antagonists: A Systematic Review and Meta-analysis and Meta-regression. *Anesth. Analg.* **2016**, *123*, 977–988. [CrossRef]
10. Tubog, D.T.; Bramble, R.S. Ondansetron reduces the incidence of hypotension after spinal anaesthesia in non-caesarean delivery: A systematic review and meta-analysis. *J. Perioper. Pract.* **2022**, *32*, 29–40. [CrossRef]
11. Mohamed, S.; Befkadu, A.; Mohammed, A.; Neme, D.; Ahmed, S.; Yimer, Y.; Girma, T. Effectiveness of prophylactic ondansetron in preventing spinal anesthesia induced hypotension and bradycardia in pregnant mother undergoing elective cesarean delivery: A double blinded randomized control trial, 2021. *Int. J. Surg. Open* **2021**, *35*, 100401. [CrossRef]
12. Mendonça, F.T.; Crepaldi, L.C., Jr.; Gersanti, R.C.; de Araújo, K.C. Effect of ondansetron on spinal anesthesia-induced hypotension in non-obstetric surgeries: A randomised, double-blind and placebo-controlled trial. *Braz. J. Anesthesiol.* **2021**, *71*, 233–240. [CrossRef] [PubMed]
13. Bhiwal, A.K.; Chauhan, K.; Choudhary, S.; Bhatt, H.A.; Gupta, S. Intravenous Ondansetron to Prevent Hypotension During Cesarean Section Under Spinal Anaesthesia. *J. Obstet. Anaesth. Crit. Care* **2021**, *11*, 15–19. [CrossRef]
14. Patel, P.C.; Parmar, D.; Patel, U.; Shah, R.S. Comparison of Injection Granisetron versus Injection Ondansetron for Control of Intraoperative Nausea and Vomiting and Post-Operative Nausea and Vomiting among the Women Undergoing Lower Segment Caesarean Section under Spinal Anaesthesia. *Adv. Hum. Biol.* **2021**, *11*, 172–175.
15. Wetterslev, J.; Jakobsen, J.C.; Gluud, C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med. Res. Methodol.* **2017**, *17*, 39. [CrossRef] [PubMed]
16. Ogah, J.; Otegbeye, A.U. Attenuating Spinal-Induced Hypotension with Ondansetron in Parturients Undergoing Casarean Section. *Anesth. Analg.* **2021**, *132*, 596.
17. Brahim, A.; Ben Lamine, F.; Abdelmoula, H.; Ben Jazia, K. Ondansetron, dexamethasone and their combination compared for the prevention of nausea and vomiting during a caesarean section under spinal anesthesia. *Anesth. Analg.* **2021**, *133*, 1030.
18. Uerpairojkit, K.; Chesoh, A.; Budcharoentong, D. Ondansetron for Prophylaxis of Spinal Morphine Induced Nausea during Early Rooming in Breastfeeding: A Randomized Placebo Controlled Trial. *Anesth. Analg.* **2016**, *123*, 286–287. [CrossRef]
19. Samarah, W.K.; Alghanem, S.M.; Bsisu, I.K.; Rahman, Z.A.; Guzu, H.A.; Abufares, B.N. The effect of ondansetron administration 20 minutes prior to spinal anaesthesia on haemodynamic status in patients undergoing elective caesarean section: A comparison between two different doses. *Indian J. Anaesth.* **2020**, *64*, 954–959.
20. Moro, E.T.; Teixeira Ferreira, M.A.; dos Santos Goncalves, R.; Vargas, R.C.; Calil, S.J.; Soranz, M.A.; Bloomstone, J. The Quality of Recovery after Dexamethasone, Ondansetron, or Placebo Administration in Patients Undergoing Lower Limbs Orthopedic Surgery under Spinal Anesthesia Using Intrathecal Morphine. A Randomized Controlled Trial. *Anesthesiol. Res. Pract.* **2020**, *2020*, 9265698. [CrossRef]
21. Hulchafo, A.; Abiy, S.; Shifa, S.; Yemam, D. Effectiveness of prophylactic intravenous ondasetron to reduce fentanyl induced pruritus among elective cesarean section patients in Worabe Comprehensive Specialized Hospital, Southern Ethiopia, 2020, randomized clinical trial. *Int. J. Surg. Open* **2020**, *24*, 52–56. [CrossRef]
22. Rasooli, S.; Moslemi, F.; Gogazadeh, M. Preventing Nausea and Vomiting Using Ondansetron and Metoclopramide-Phenylephrine in Cesarean Section Using Spinal Anesthesia. *Crescent J. Med. Biol. Sci.* **2019**, *6*, 61–65.
23. Oliveira Campos, G.; de Jesus Martins, M.; Jesus, G.N.; Rios de Oliveira, P.R.; Lessa, C.N.; Macedo Fernandes de Oliveira, J.C., Jr.; de Castro Alves, L.J.S.; Alves, R.L.; Módolo, N.S.P. Palonosetron versus ondansetron for prevention of nausea and vomiting after total abdominal hysterectomy under spinal anesthesia with intrathecal morphine: A double-blind, randomized controlled trial. *BMC Anesthesiol.* **2019**, *19*, 159.
24. Shokrpour, M.; Homayuni, S.; Kamali, A.; Pazuki, S. Comparing the prophylactic effect of ondansetron and dexamethasone in controlling headaches caused by spinal anesthesia among women candidated for caesarean A randomized controlled trial. *Electron. J. Gen. Med.* **2018**, *15*, 6.
25. Suman, B.R.; Umesh, R.; Rohan, B. A Comparative Study of Intravenous Ondansetron, Granisetron and Ramosetron for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Caesarean Section. *J. Evol. Med. Dent. Sci.-JEMDS* **2017**, *6*, 575–580. [CrossRef]
26. Ghanei, M.; Damshenas, M.H.; Radmehr, M.; Kalani, N.; Rastgarian, A. Comparison of the Effects of Pethidine and Ondansetron in Prevention of Shivering after Spinal Anesthesia for Cesarean Section: A Double-Blind Clinical Trial. *J. Fundam. Appl. Sci.* **2017**, *9*, 1134–1142.
27. Badawy, A.A.; Mokhtar, A.M. The role of ondansetron in prevention of post-spinal shivering (PSS) in obstetric patients: A double-blind randomized controlled trial. *Egypt. J. Anaesth.* **2017**, *33*, 29–33. [CrossRef]
28. Rai, S.; Verma, S.; Pandey, H.P.; Yadav, P.; Patel, A. Role of butorphanol and ondansetron premedication in reducing postoperative shivering after general and spinal anesthesia: A randomized comparative study from North India. *Anesth. Essays Res.* **2016**, *10*, 319–323. [CrossRef]
29. Moustafa, A.A.; Baaror, A.S.; Abdelazim, I.A. Comparative study between nalbuphine and ondansetron in prevention of intrathecal morphine-induced pruritus in women undergoing cesarean section. *Anesth. Essays Res.* **2016**, *10*, 238–244.

30. Bommala, S.; Mukkara, M.; Samantaray, A.; Pasupuleti, H.; Reddycogu, D.M.; Pudotha, S.S.; Shravani, P.; Sathish. Effects of Intravenous Odansetron and Granisetron on Haemodynamic Changes during Spinal Anaesthesia in Non-obstetric Population: A Randomised Double Blind Study. *J. Clin. Diagn. Res.* **2019**, *13*, UC01–UC4.
31. Haroon, M. Effectiveness of Prophylactic Venous Management of Ondansetron for Anticipation of Backbone Anesthesia Encouraged Hypotension in Aged Respondents. *Indo Am. J. Pharm. Sci.* **2019**, *6*, 11855–11858.
32. Kelsaka, E.; Baris, S.; Karakaya, D.; Sarihasan, B. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. *Reg. Anesth. Pain Med.* **2006**, *31*, 40–45. [CrossRef] [PubMed]
33. Marciniak, A.; Owczuk, R.; Wujtewicz, M.; Preis, K.; Majdyło, K. The influence of intravenous ondansetron on maternal blood haemodynamics after spinal anaesthesia for caesarean section: A double-blind, placebo-controlled study. *Ginekol. Pol.* **2015**, *86*, 461–467. [CrossRef] [PubMed]
34. Mohamed, S.A.; Hussam, A.M.; Abdallah, S.A.; Sarhan, K.A.; Shaban, A.M. Ondansetron Is an Effective Alternative to Decrease the Incidence of Postspinal Hypotension in Healthy Subjects Undergoing Infra-Umbilical Surgeries Compared to Combined Volume Loading and Vasoconstrictors: Randomized Controlled Trial. *Open Access Maced. J. Med. Sci.* **2018**, *6*, 2363–2368. [CrossRef] [PubMed]
35. Mohammadzadeh Jouryabi, A.; Sharami, S.H.; Mansour Ghanaie, M.; Sedighinejad, A.; Imantalab, V.; Rafiee Sorouri, Z.; Biazar, G.; Nobijari, T.Z. Comparing the Effects of Low Dose of Ketamine, Tramadol, and Ondansetron in Prevention of Post Spinal Anesthesia Shivering in Cesarean Section. *Anesthesiol. Pain Med.* **2021**, *11*, e116429. [CrossRef] [PubMed]
36. Nallam, S.R.; Cherukuru, K.; Sateesh, G. Efficacy of Intravenous Ondansetron for Prevention of Postspinal Shivering during Lower Segment Cesarean Section: A Double-Blinded Randomized Trial. *Anesth. Essays Res.* **2017**, *11*, 508–513. [CrossRef] [PubMed]
37. Ortiz-Gómez, J.R.; Palacio-Abizanda, F.J.; Morillas-Ramirez, F.; Fornet-Ruiz, I.; Lorenzo-Jiménez, A.; Bermejo-Albares, M.L. The effect of intravenous ondansetron on maternal haemodynamics during elective caesarean delivery under spinal anaesthesia: A double-blind, randomised, placebo-controlled trial. *Int. J. Obstet. Anesth.* **2014**, *23*, 138–143. [CrossRef]
38. Owczuk, R.; Wenski, W.; Polak-Krzeminska, A.; Twardowski, P.; Arszułowicz, R.; Dylczyk-Sommer, A.; Wujtewicz, M.A.; Sawicka, W.; Morzuch, E.; Smietanski, M.; et al. Ondansetron given intravenously attenuates arterial blood pressure drop due to spinal anesthesia: A double-blind, placebo-controlled study. *Reg. Anesth. Pain Med.* **2008**, *33*, 332–339.
39. Owczuk, R.; Wenski, W.; Twardowski, P.; Dylczyk-Sommer, A.; Sawicka, W.; Wujtewicz, M.A.; Marciniak, A.; Polak-Krzemińska, A.; Jasiński, T.; Wujtewicz, M. Ondansetron attenuates the decrease in blood pressure due to spinal anesthesia in the elderly: A double blind, placebo-controlled study. *Minerva Anestesiol.* **2015**, *81*, 598–607.
40. Pirat, A.; Tuncay, Ş.F.; Torgay, A.; Candan, S.; Arslan, G. Ondansetron, orally disintegrating tablets versus intravenous injection for prevention of intrathecal morphine-induced nausea, vomiting, and pruritus in young males. *Anesth. Analg.* **2005**, *101*, 1330–1336. [CrossRef]
41. Ramon Ortiz-Gomez, J.; Javier Palacio-Abizanda, F.; Morillas-Ramirez, F.; Fornet-Ruiz, I.; Lorenzo-Jimenez, A.; Lourdes Bermejo-Albares, M. Reducing by 50% the incidence of maternal hypotension during elective caesarean delivery under spinal anesthesia: Effect of prophylactic ondansetron and/or continuous infusion of phenylephrine—A double-blind, randomized, placebo controlled trial. *Saudi J. Anaesth.* **2017**, *11*, 408–414. [CrossRef] [PubMed]
42. Rashad, M.M.; Farmawy, M.S. Effects of intravenous ondansetron and granisetron on hemodynamic changes and motor and sensory blockade induced by spinal anesthesia in parturients undergoing cesarean section. *Egypt. J. Anaesth.* **2013**, *29*, 369–374. [CrossRef]
43. Safavi, M.; Honarmand, A.; Negahban, M.; Attari, M. Prophylactic effects of intrathecal Meperidine and intravenous Ondansetron on shivering in patients undergoing lower extremity orthopedic surgery under spinal anesthesia. *J. Res. Pharm. Pract.* **2014**, *3*, 94–99. [PubMed]
44. Sahoo, T.; SenDasgupta, C.; Goswami, A.; Hazra, A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomised, placebo-controlled study. *Int. J. Obstet. Anesth.* **2012**, *21*, 24–28. [CrossRef]
45. Shakya, S.; Chaturvedi, A.; Sah, B.P. Prophylactic low dose ketamine and ondansetron for prevention of shivering during spinal anaesthesia. *J. Anaesthesiol. Clin. Pharmacol.* **2010**, *26*, 465–469.
46. Tatikonda, C.M.; Rajappa, G.C.; Rath, P.; Abbas, M.; Madhapura, V.S.; Gopal, N.V. Effect of Intravenous Ondansetron on Spinal Anesthesia-Induced Hypotension and Bradycardia: A Randomized Controlled Double-Blinded Study. *Anesth. Essays Res.* **2019**, *13*, 340–346. [CrossRef]
47. Terkawi, A.S.; Tiouririne, M.; Mehta, S.H.; Hackworth, J.M.; Tsang, S.; Durieux, M.E. Ondansetron Does Not Attenuate Hemodynamic Changes in Patients Undergoing Elective Cesarean Delivery Using Subarachnoid Anesthesia: A Double-Blind, Placebo-Controlled, Randomized Trial. *Reg. Anesth. Pain Med.* **2015**, *40*, 344–348. [CrossRef]
48. Trabelsi, W.; Romdhani, C.; Elaskri, H.; Sammoud, W.; Bensalah, M.; Labbene, I.; Ferjani, M. 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. *Anesthesiol. Res. Pract.* **2015**, *2015*, 158061. [CrossRef]
49. Wang, M.; Zhuo, L.; Wang, Q.; Shen, M.K.; Yu, Y.Y.; Yu, J.J.; Wang, Z.-P. Efficacy of prophylactic intravenous ondansetron on the prevention of hypotension during cesarean delivery: A dose-dependent study. *Int. J. Clin. Exp. Med.* **2014**, *7*, 5210–5216.

50. Wang, Q.; Zhuo, L.; Shen, M.K.; Yu, Y.Y.; Yu, J.J.; Wang, M. Ondansetron preloading with crystalloid infusion reduces maternal hypotension during cesarean delivery. *Am. J. Perinatol.* **2014**, *31*, 913–922. [CrossRef]
51. Chooi, C.; Cox, J.J.; Lumb, R.S.; Middleton, P.; Chemali, M.; Emmett, R.S.; Middleton, P.; Simmons, S.W. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst. Rev.* **2020**, *7*, Cd002251. [CrossRef] [PubMed]
52. Fitzgerald, J.P.; Fedoruk, K.A.; Jadin, S.M.; Carvalho, B.; Halpern, S.H. Prevention of hypotension after spinal anaesthesia for caesarean section: A systematic review and network meta-analysis of randomised controlled trials. *Anaesthesia* **2020**, *75*, 109–121. [CrossRef] [PubMed]
53. Eldaba, A.A.; Amr, Y.M. Intravenous granisetron attenuates hypotension during spinal anesthesia in cesarean delivery: A double-blind, prospective randomized controlled study. *J. Anaesthesiol. Clin. Pharmacol.* **2015**, *31*, 329–332.
54. Tubog, T.D.; Kane, T.D.; Pugh, M.A. Effects of Ondansetron on Attenuating Spinal Anesthesia–Induced Hypotension and Bradycardia in Obstetric and Nonobstetric Subjects: A Systematic Review and Meta-Analysis. *AANA J.* **2017**, *85*, 113–122. [PubMed]
55. Gao, L.; Zheng, G.; Han, J.; Wang, Y.; Zheng, J. Effects of prophylactic ondansetron on spinal anesthesia-induced hypotension: A meta-analysis. *Int. J. Obstet. Anesth.* **2015**, *24*, 335–343. [CrossRef]
56. Heesen, M.; Stewart, A.; Fernando, R. Vasopressors for the treatment of maternal hypotension following spinal anaesthesia for elective caesarean section: Past, present and future. *Anaesthesia* **2015**, *70*, 252–257. [CrossRef] [PubMed]