Effect of ondansetron on spinal anesthesia-induced hypotension in non-obstetric surgeries: a randomised, double-blind and placebo-controlled trial

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Abstract
Background and objectives: Spinal anesthesia is an effective technique for many surgical procedures, but it is often associated with an increased risk of potentially deleterious hemodynamic disturbances. The benefits of prophylactic ondansetron for preventing spinal anesthesia-induced hypotension are still uncertain. Therefore, this study aimed to compare the effect of ondansetron and placebo before spinal block on the incidence of hypotension in patients having non-obstetric surgeries.

Methods: Randomized, double-blind, parallel-group, superiority trial with a 1:1 allocation ratio. A total of 144 patients scheduled for non-obstetric surgeries with an indication for spinal anesthesia were randomized. Patients received intravenous ondansetron (8 mg) or placebo before standard spinal anesthesia. The primary outcome was the rate of hypotension in the first 30 minutes after spinal anesthesia.

Results: Hypotension occurred in 20 of 72 patients (27.8%) in the ondansetron group and in 36 of 72 patients (50%) in the placebo group (Odds Ratio–OR = 0.38; 95% Confidence Interval–CI 0.19 to 0.77; p = 0.007). Fewer patients in the ondansetron group required ephedrine compared to the placebo group (13.9% vs. 27.8%; OR = 0.42; 95% CI 0.18 to 0.98; p = 0.04). Exploratory analyses revealed that ondansetron may be more effective than placebo in patients aged 60 years or older (OR = 0.12; 95% CI 0.03 to 0.48; p = 0.03). No difference in heart rate variations was observed.

Conclusion: Our findings suggest that ondansetron can be a viable and effective strategy to reduce both the incidence of spinal anesthesia-induced hypotension and vasopressors usage in non-obstetric surgeries.

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Introduction

Besides being the most common anesthesia technique for cesarean section, spinal anesthesia has become the anesthetic approach of choice for many general surgical procedures on the lower limbs, perineum and lower abdomen. This technique is of easy execution, providing not only fast intraoperative anesthesia with a lower respiratory impact, but also better pain control, favoring a rapid recovery.\textsuperscript{1,2} Despite its many advantages, spinal anesthesia has important side effects including hypotension, which is observed in approximately 40\% of non-obstetric patients and 80\% of the obstetric patients.\textsuperscript{3,4} Arterial hypotension can lead to a reduction in blood flow and cardiac output, resulting in a state of systemic hypoperfusion. Following spinal anesthesia, hypotension results mainly from a decrease in systemic vascular resistance secondary to a blockage of sympathetic fibers and an increase in vagal tone. This reduction in venous return can trigger the Von Bezold-Jarisch (BJ) reflex, mediated by serotonin receptors (subtype 5-HT\textsubscript{3}), resulting in increased efferent vagal signaling and bradycardia, ultimately exacerbating hypotension.\textsuperscript{1,5-7} Importantly, if associated with bradycardia and without proper treatment, hypotension can progress to cardiac arrest.\textsuperscript{8} Thus, therapeutic strategies that can reduce the risk of hypotension after spinal anesthesia may prevent more critical side effects related to this technique.\textsuperscript{9}

Ondansetron is a drug employed as prophylaxis for Postoperative Nausea and Vomiting (PONV), whose antiemetic activity involves the selective inhibition of the 5-HT\textsubscript{3} receptors.\textsuperscript{10} As a result, ondansetron can suppress the BJ reflex, and it has been postulated as a therapeutic strategy to prevent hypotension in patients undergoing spinal anesthesia.\textsuperscript{6,11} In this respect, several studies have demonstrated the effectiveness of ondansetron on obstetric patients.\textsuperscript{6,11-13} However, only a few trials have investigated the prophylactic use of ondansetron to prevent hypotension after spinal anesthesia in non-obstetric patients.\textsuperscript{7,14}

The aim of the present study was, therefore, to assess whether the intravenous administration of ondansetron before spinal anesthesia is more effective to reduce the incidence of hypotension in patients undergoing non-obstetric surgical procedures compared to placebo.

Methods

Trial design and trial setting

This was a prospective, randomized, parallel-group, superiority placebo-controlled, faze IV trial with a 1:1 allocation ratio carried out at the Hospital de Base do Distrito Federal, Brasília, Distrito Federal, Brazil, from March 2019 to December 2019. The study was approved by the local Research Ethics Committee (Comitê de Ética em Pesquisa do Instituto de Gestão Estratégica de Saúde do Distrito Federal–CEP/IGESDF, Brasília, DF, Brazil) on February 26, 2019, with record number 3.172.436, and registered in the Plataforma Brazil (http://aplicacao.saude.gov.br/plataformabrasil) under the number CAAE 03627118.3.0000.8153, and at Clinical Trials (NCT03973411). All patients gave formal written informed consent, and all information were deidentified. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

We included patients that were scheduled for urgent or elective surgical procedures requiring spinal anesthesia. Surgeries from all medical specialties were allowed. Eligible patients were 18 years of age or older with American Society of Anesthesiologists (ASA) physical status I, II, or III. Exclusion criteria were patients with any contraindication or a history of hypersensitivity to the drugs used in the study, use of clonidine during the spinal anesthesia, patients using prophylactic or therapeutic anticoagulation treatments. We also excluded patients with atrioventricular block in any degree, diagnosed with cardiac arrhythmias, heart failure patients, kidney disease, liver diseases, any type of suspected systemic or localized infection at the puncture site, or any contraindication to the neuroaxial anesthesia.

Interventions

In the operating room, all patients received standard monitoring, which included electrocardiography, pulse oxygen saturation, noninvasive blood pressure monitoring, and body temperature. After venous access, patients received 0.05 mg.kg\textsuperscript{-1} midazolam Intravenous (IV). Crystalloids were administered at a volume of 10 mL.kg\textsuperscript{-1} before to spinal anesthesia. Deidentified syringes (20 mL) containing either ondansetron (6 mg) or placebo (distilled water) was delivered to the theatre and administered 5 minutes before spinal anesthesia, which was then performed with hyperbaric bupivacaine (15 mg or more), and adjuvant opioids at the discretion of the anesthesiologist, except clonidine. Spinal anesthesia was performed in a sitting position and patients were placed in a supine position immediately after the injection. Patients remained in a supine position for the duration of the study (30 minutes). After this period, the surgery was started.

Outcomes

The primary outcome was the proportion of patients with hypotension during surgery. Hypotension was defined as systolic blood pressure (SBP) below 80\% of control or below 90 mmHg. Secondary outcomes included the proportion of patients with bradycardia, vasopressor usage, and variations in blood pressure and Heart Rate (HR). Baseline SBP and HR values were recorded, as well as after anxiolysis, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes after spinal anesthesia. We calculated the difference between the highest and lowest systolic blood pressure and heart rate (reported as change in SBP and HR) and identified the lowest value noted during the study time. Bradycardia was defined as an HR of below 50 beats/min. Patients were also given atropine 0.5 mg in case of bradycardia and ephedrine 5 mg in case of hypotension. All patients received oxygen (100\%) through a face mask after spinal anesthesia.
Sample size

Based on data from a pilot study, we assumed that 45% of the patients would have hypotension after spinal anesthesia. Moreover, we hypothesized that treatment with ondansetron would result in a 30% risk difference in the rate hypotension compared to placebo (15% vs. 45%). Thus, a sample size of 100 patients (50 per group) was initially planned to give the trial 90% power an alpha level of 5% (two-sided). However, the sample size was recalculated with the availability of trial data, and we updated sample size parameters for a more conservative treatment difference (17.5% vs. 45%). Allowing for a potential 20% dropout rate, we calculated that 70 patients per group (a total of 140) would be required to give the trial 90% power to detect this updated treatment difference. Sample size calculations were performed with the web platform (https://clinicalcalc.com/stats/samplesize.aspx).

Randomization sequence, allocation concealment

We used a computer-generated, centrally concealed 1:1 randomization sequence. An independent investigator not involved in patient surgery or follow-up generated the random sequence list and randomly allocated patients into two groups via the Sequentially Numbered Opaque Sealed Envelopes (SNOSE) technique. Syringes containing either ondansetron or placebo were prepared centrally by the same investigator, pre-coded, and sent sequentially to the surgical room right before its administration.

Blinding

This is a double-blind study at the level of patients, care providers, and outcome assessors. Anesthesiologists, surgeons, and operating personnel did not know which study treatment was used. Syringes were identical in terms of volume, color, viscosity, and odor.

Statistical methods

Normality assumptions were assessed with the Shapiro-Wilk test. Between-group differences at baseline were examined with Chi-Square or Fisher’s Exact tests for binary and categorical outcomes. Continuous variables were compared via unpaired Student’s t-tests. A logistic-regression model was fitted with binary dependent variables and stratified according to age. We used linear mixed-effects models to examine the effect of ondansetron vs. placebo over time. Fixed effects were time and treatment group. Time was included in the models as a categorical variable. Models were constructed with interactions terms between time and treatment group and had a random intercept for each patient. Holm-Šidák correction was applied for multiple comparisons. In a non-prespecified analysis, we fitted the same models with interaction terms for time, treatment, and age, defined as a binary variable (≥ 60 years vs. < 60 years).15 A two-tailed p < 0.05 was considered statistically significant. Analyses were based on the Intention-To-Treat (ITT) principle, in which all randomized patients were included in the analyses as randomized and contributed to the analyses. Results are summarized as mean (Standard Deviation–SD), mean (95% Confidence Interval–95% CI), mean difference (95% CI), counts (percentage), or Odds Ratio (OR) with 95% CI. All analyses were performed with Stata 16.0 (CollegeStation, TX, USA).

Subgroup analyses

Based on clinical grounds, we performed a non-prespecified subgroup analysis comparing elderly patients (60 years of age or older) to non-elderly patients (< 60 years of age).

Results

From July 2019 through December 2019, we screened a total of 188 patients for eligibility. Of these, 144 met all inclusion criteria and were randomized (72 per group). Four patients in the placebo group received a dose of hyperbaric bupivacaine below the recommended by the study protocol, but they were included in the ITT analysis (Figure 1). Overall, both groups were comparable with respect to demographic and baseline clinical characteristics (Table 1). No deaths or serious complications occurred.

Primary outcomes

The risk of hypotension was 27.8% (20 of 72 patients) in the ondansetron group and 50% (36 of 72 patients) in the placebo group (OR = 0.38; 95% CI 0.19 to 0.77; p = 0.007) (Table 2).

Secondary outcomes

Fewer patients in the ondansetron group required ephedrine compared to the placebo group (13.9% [10 of 72 patients] vs. 27.8% [20 of 72 patients]; OR = 0.42; 95% CI 0.18 to 0.98; p = 0.04) (Table 2). Other pre-specified secondary outcomes, such as blood pressure levels at 5, 10, 15, 20, and 30 minutes after anxiolysis, did not differ substantially between the two groups (Table 2). No secondary outcomes remained statistically significant after a Holm-Šidák multiple testing correction.

Subgroup analyses

For the primary outcome, elderly patients demonstrated a greater benefit with ondansetron compared to younger patients (p = 0.03 for interaction) (Figure 2). Hypotension occurred in 5 out of 18 elderly patients (27.8%) in the ondansetron group and in 19 out of 25 elderly patients in the placebo group (76%) (OR = 0.12; 95% CI 0.03 to 0.48; p = 0.003). In the non-elderly subgroup, hypotension occurred in 15 out of 54 patients (27.8%) in the ondansetron group and in 17 out of 47 patients (36.2%) in the placebo group (OR = 0.68; 95% CI 0.29 to 1.58; p = 0.37) (Supplementary Tables S1 and S2). This age-related interaction effect was not observed in any secondary outcome.
It is important to understand the clinical significance of these findings. For example, in a recent study, researchers evaluated the effect of ondansetron vs. placebo in patients undergoing spinal anesthesia. The results showed that ondansetron significantly reduced the incidence of hypotension compared to placebo. This finding is consistent with previous studies that have demonstrated the efficacy of ondansetron in preventing postoperative hypotension.

In the discussed study, ondansetron was found to be effective in preventing hypotension in patients undergoing spinal anesthesia. However, it is important to note that the clinical significance of this finding may vary depending on the patient population and the specific surgical procedure performed. For example, in patients undergoing major abdominal surgery, the risk of hypotension may be higher and therefore, the potential benefits of ondansetron may be greater. On the other hand, in patients undergoing minor procedures, the risk of hypotension may be lower and the potential benefits of ondansetron may be smaller.

In conclusion, the results of this study highlight the potential benefits of ondansetron in preventing hypotension in patients undergoing spinal anesthesia. However, further research is needed to evaluate the long-term effects of ondansetron and its impact on clinical outcomes. Additionally, considering the potential side effects of ondansetron, it is important to carefully weigh the benefits and risks of its use in different patient populations.
Table 1  Baseline demographic and clinical characteristics of the study participants.

|                      | Placebo (n = 72) | Ondansetron (n = 72) |
|----------------------|------------------|----------------------|
| Age, mean (SD), y    | 51.0 (17.3)      | 47.4 (16.5)          |
| Height, mean (SD), cm| 166.7 (6.8)      | 169.7 (9.5)          |
| Weight, mean (SD), kg| 72.2 (17.8)      | 72.7 (13.5)          |
| Males, n (%)         | 41 (56.9)        | 49 (68.1)            |
| ASA, n (%)           |                  |                      |
| I                    | 14 (19.4)        | 21 (29.2)            |
| II                   | 46 (63.4)        | 40 (55.6)            |
| III                  | 12 (16.7)        | 11 (15.3)            |
| Hypertension, n (%)  | 25 (34.7)        | 23 (31.9)            |
| ACE inhibitors or ARBs usage, n (%) | 23 (31.9) | 18 (25.0) |
| Type-2 diabetes, n (%)| 13 (18.1)      | 11 (15.3)            |
| Obesity, n (%)       | 8 (11.1)         | 10 (13.9)            |
| Elderly, n (%)       | 25 (34.7)        | 18 (25.0)            |
| Medical specialty, n (%) |                |                      |
| General surgery      | 4 (5.6)          | 2 (2.8)              |
| Oncological surgery  | 3 (4.2)          | 2 (2.8)              |
| Vascular surgery     | 13 (18.1)        | 7 (9.7)              |
| Urology              | 13 (18.1)        | 20 (27.8)            |
| Proctology           | 6 (8.3)          | 4 (5.6)              |
| Gynecology           | 2 (2.8)          | 3 (4.2)              |
| Orthopedics          | 31 (43.1)        | 34 (47.2)            |
| Bupivacaine, mean (SD), mg | 15.4 (2.7) | 16.0 (2.6) |
| Morphine usage, n (%)| 61 (84.7)        | 61 (84.7)            |
| Morphine dose, mean (SD), mcg | 94.4 (24.4) | 92.3 (16.1) |
| Analgesia level, n (%) |            |                      |
| T4                   | 5 (6.9)          | 2 (2.8)              |
| T6                   | 21 (29.2)        | 19 (26.4)            |
| T8                   | 20 (27.8)        | 18 (25)              |
| T10                  | 24 (33.3)        | 23 (31.9)            |
| T12                  | 2 (2.8)          | 10 (13.9)            |

ASA, American Society of Anesthesiologists physical status; SD, Standard Deviation. ACE, Angiotensin-Converting Enzyme; ARBs, Angiotensin Receptor Blockers.

spinal anesthesia due to its vasoconstriction-inhibiting properties. Another mechanism exists during spinal anesthesia, the reverse Bainbridge reflex.  During high and low spinal anesthesia, BP, HR and right atrial pressure are all decreased in the same proportion, and the intensity of bradycardia is proportional to the drop in BP. Concerning this reverse Bainbridge reflex, the pathway shares the same vagal way than BJ, but this reverse BR facilitates vagal outflow and inhibits sympathetic outflow to the sinoatrial node causing bradycardia. If 5-HT3 are associated with cardioreceptors involved in the BR response to inhibit sympathetic neurons at the level of the brainstem, other systems are potentially associated with the physiology of hypotension/low heart rate during spinal anesthesia. The Medial Septum/vertical limb of the Diagonal Band complex (MSDB) influences the hippocampus through projections from cholinergic, GABAergic, and glutamatergic neurons, and is implicated in the control of BP. 5-HT3 receptors at the MSDB produce a tonic inhibitory action of the sympathetic pathway that is mediated via the local release of angiotensin in the MS/vDB. 

From a physiological point of view, during spinal anesthesia, the cardioinhibitory afferents fibers act as a protective effect to counteract the redistributive hypovolemic state and do not represent, strictly speaking, a pure BJ reflex. These effects can occur at any point during anesthesia may progress to cardiac arrest without proper treatment. Thus, the identification of therapeutic strategies that efficiently prevent these reflexes in patients undergoing spinal anesthesia can be highly valuable for anesthesiologists.

Herein, we showed that the prophylactic administration of ondansetron is an attractive alternative to decrease the incidence of hypotension induced by spinal anesthesia in non-obstetric patients. Most notably, we show that this effect was significantly evident in elderly patients (≥ 60 years). Consistent with previous reports showing that ondansetron prevents complications related to spinal blockade in geriatric patients, we also observed that the administration of ondansetron prior to anesthesia prevents hypotension without affecting the heart rate of these patients. In older patients, inflammation, oxidative stress, and endothelial dysfunction can lead to an increased in arterial stiffness and a decreased vascular distensibility. The consequences are higher SBP and pulse pressure levels, augmented left ventricular contraction and afterload, as well as a reduction in coronary perfusion and left ventricular early diastolic filling. We observed that patients aged over 60 years displayed higher baseline SBP levels and a greater mean change than younger. Aging is also associated with a decreased response to beta-adrenergic drugs and an increase in the parasympathetic state which, in turn, attenuates cardiopulmonary reflex and baroreflex. A previous study on low-dose spinal anesthesia study detected a higher drop in cardiac index, left ventricular stroke volume and systemic vascular resistance in older patients compared to younger. Another plausible explanation for these results relies on the fact that approximately 80% of the blood volume is stored in veins and that age-related vessel stiffening may dampen the ability to cushion changes in blood volume, such as that caused by vasodilation during spinal anesthesia.

Moreover, we cannot fully exclude that the preventive effect observed predominantly in the elderly group might be because these patients are more susceptible to hypotension induced by the BJ reflex. In line with this hypothesis, it is recognized that geriatric patients usually display decreased blood flow from the superior and inferior vena cava that is gradually intensified with advancing age. The decrease in blood flow related to vascular stiffness associated with the vasodilation provoked by neuraxial block could explain the important reduction in preload in geriatric patients and justify why the BJ reflex is more active in this group of patients. Thus, it is conceivable that ondansetron would be more effective in preventing hypotension induced by spinal anesthesia in elderly patients by blocking this reflex.

Previous studies involving obstetric patients observed that patients that received 4mg of ondansetron before to subarachnoid block had a lower incidence of hypotension and consumption of vasopressors, suggesting the involvement of the inhibition of the BJ reflex. While our trial was conducted with a non-obstetric population, it is still possible to draw a parallel between pregnant women and the elderly since both have an important physiological reduction.
in preload, which reinforces the idea that the suppression of the BJ reflex would explain the results observed in our study.

Nonetheless, this hypothesis is challenged by a previous study, which shows that ondansetron prevents postoperative hypotension of elderly patients undergoing general anesthesia. In that study, geriatric patients received standard anesthetic induction that was maintained by inhaled anesthetics. Strikingly, while 45% of the control patients presented postoperative hypotension, this complication was observed in only 16% of the patients receiving 4 mg of intravenous ondansetron. The exact mechanism of this effect after general anesthesia remains to be determined and cannot be explained by suppressing the BJ reflex. Therefore, whether the prophylactic effect in mitigating postoperative hypotension related to spinal anesthesia, detected in our trial, is a consequence of the inhibition of the BJ and/or other cardiovascular tone-related mechanism remains unclear.

A previous meta-analysis that included 17 randomized trials with a total of 1,604 participants have indicated that 5-HT3 antagonists are effective in reducing the incidence of hypotension and bradycardia, but these effects were limited only to patients undergoing cesarean section, which seemingly contradicts the effect we observed in our study. However, only 3 out of 9 studies that included non-obstetric patients imposed no age limit for enrollment, accepting both ASA I or II patients. Similarly, another meta-analysis performed with data from 14 randomized trials encompassing data from 1,045 patients concluded there is no solid evidence to confirm that ondansetron reduces the incidence of hypotension and bradycardia after subarachnoid anesthesia. Of note, only one among the 14 included studies had examined the effect of ondansetron in patients aged 60 years or older and, thus, their conclusion is based primarily on non-elderly participants. Accordingly, a more recent double-blind, randomized, placebo-controlled study with patients between 20 and 60 years old, totaling 140 patients, reported that participants receiving ondansetron prior to neuraxial block had similar blood pressure and heart rate compared to placebo. Our study also found no effect on hypotension and bradycardia in young non-obstetric patients receiving ondansetron. It is likely that, despite the sympathetic block, the adequate venous return of these patients, due to an effective venoconstriction, will be able to maintain the preload, making the Bezold Jarish reflex less relevant in this patient population.

Despite our findings, this trial possesses some limitations worth mentioning. First, we did not assess clinical outcomes that occurred outside the operating room; therefore, it is not possible to infer whether intravenous administration of ondansetron before spinal block also results in better clini-
cal outcomes after surgery. Second, Postoperative Nausea and Vomiting (PONV) is a patient-relevant endpoint, but these outcomes were not considered in this trial because the effectiveness of ondansetron in the prophylaxis of PONV has been established previously. Third, the generalizability of our results for the elderly population may be limited, since older patients accounted for approximately one-third of our patients only. Fourth, the sample size for the non-prespecified subgroup analyses (elderly vs. non-elderly) is relatively small. This reduced sample size for each subgroup restricts the conclusions that can be drawn from our trial. Hence, our findings suggesting a treatment-by-age interaction should be regarded as exploratory only, and larger studies are needed to elucidate the role of ondansetron in the prevention of spinal anesthesia-induced hypotension specifically in older populations.

Conclusion

In conclusion, the prophylactic administration of ondansetron resulted in significantly lower rates of hypotension induced by spinal anesthesia when compared to placebo, especially in patients aged 60 years or older. Our results indicate not only that the prophylactic use of ondansetron can reduce the usage of ephedrine during general non-obstetric surgical procedures that require spinal anesthesia, but also that ondansetron may help to limit the side effects related to spinal block particularly in elderly patients.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2020.12.028.

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