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ONDANSETRON: BEYOND ANTIEMESIS – A PROTECTIVE ROLE AGAINST SPINAL ANAESTHESIA- INDUCED HYPOTENSION IN CAESAREAN SECTION

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ABSTRACT

Background: Spinal anaesthesia is the preferred technique for elective caesarean section due to its rapid onset, reliability, and maternal safety profile. However, spinal anaesthesia-induced hypotension (SAIH) remains a frequent and clinically significant complication, with potential adverse consequences for both mother and fetus. Ondansetron, a selective 5-HT3 receptor antagonist, has been proposed as a prophylactic agent to attenuate SAIH by modulating the Bezold–Jarisch reflex. This study aimed to evaluate the effect of intravenous ondansetron on the incidence and severity of hypotension in parturients undergoing caesarean section under spinal anaesthesia.

Materials and Methods: This prospective observational study was conducted at the Department of Anaesthesiology and Critical Care, Justice K. S. Hegde Charitable Hospital, K. S. Hegde Medical Academy, NITTE (Deemed to be University), Deralakatte, Mangaluru, from 1 June 2023 to 30 November 2024. Seventy-six participants were enrolled, with no exclusions and 38 participants in each group. Group O received intravenous ondansetron 4 mg 10 minutes before spinal anaesthesia; Group N did not receive prophylactic ondansetron. SBP, DBP, MAP, HR and SpO_2 were recorded at baseline and every 3 minutes for 30 minutes after spinal anaesthesia. Hypotension was defined using the lower of 90 mmHg and 80% of baseline SBP. Ephedrine requirements, nausea and vomiting, shivering and rhythm disturbances were assessed. Analysis used SPSS version 25, independent-samples t-tests or Mann–Whitney U tests, chi-square tests and repeated-measures ANOVA or Friedman ANOVA.

Results: All 76 participants completed the study. The studyshow higher SBP in Group O at 6 and 9 minutes ($p=0.003$ at both time points), and higher DBP and MAP at 6, 9 and 12 minutes. Ephedrine was required by 22/38 participants in Group O and 32/38 in Group N ($p=0.011$). Nausea and vomiting occurred in 2/38 versus 18/38 participants, and shivering in 5/38 versus 23/38 ($p<0.001$ for both comparisons). No rhythm disturbances were reported in either group. The study narrative reports hypotension in 11 versus 28 participants, but these totals require reconciliation with the time-point counts and ephedrine-use data before a patient-level incidence estimate is presented.

Conclusion: In this observational study, prophylactic intravenous ondansetron was associated with higher blood pressure at selected early time points, lower ephedrine requirements, and less intraoperative nausea, vomiting and shivering. The observational design does not establish causality. Larger controlled studies are needed, and the study's hypotension counts require reconciliation before definitive incidence claims are made.

KEYWORDS: Ondansetron; spinal anaesthesia; hypotension; caesarean section; 5-HT3 antagonist; Bezold–Jarisch reflex; vasopressor; maternal outcomes; observational study.

INTRODUCTION

Spinal anaesthesia has become the gold standard for elective caesarean section, offering rapid onset, dense sensory and motor blockade, and a favorable safety profile for both mother and fetus.[1–3] Despite these advantages, spinal anaesthesia-induced hypotension (SAIH) remains a persistent and clinically significant complication, with reported incidence rates ranging from 55% to 90% in obstetric populations, depending on the definition and preventive strategies employed.[4–6] SAIH can result in maternal symptoms such as nausea, vomiting, dizziness, and, in severe cases, loss of consciousness.[1–3] More importantly, it may compromise uteroplacental perfusion, leading to fetal hypoxia, acidosis, and adverse neonatal outcomes.[1–3]

The pathophysiology of SAIH is multifactorial.[4–6] The primary mechanism involves sympathetic blockade, resulting in decreased systemic vascular resistance and venous return.[7–9] In pregnant women, this effect is exacerbated by aortocaval compression from the gravid uterus, further reducing preload and cardiac output.[1–3] Additionally, the activation of the Bezold–Jarisch reflex—a cardioinhibitory reflex mediated by serotonin-sensitive 5-HT3 receptors on cardiac vagal afferents—can trigger paradoxical bradycardia and vasodilation in response to sudden reductions in ventricular filling.[7–9] This reflex is particularly relevant in the context of spinal anaesthesia, where abrupt decreases in preload may inappropriately activate vagal responses, compounding hypotension and bradycardia.[7–9]

Traditional management of SAIH has relied on physical measures (left uterine displacement, leg elevation), fluid preloading or co-loading, and vasopressor administration (phenylephrine, ephedrine, norepinephrine).[4–6] While these interventions are variably effective, they may carry their own risks, such as fluid overload or fetal acidosis with certain

vasopressors.[1–3] In recent years, attention has turned to pharmacological modulation of the Bezold–Jarisch reflex as a novel strategy for SAIH prevention.[7–9] Ondansetron, a selective 5-HT3 receptor antagonist widely used for prophylaxis of nausea and vomiting, has been shown in several randomized controlled trials and meta-analyses to reduce the incidence of SAIH and associated bradycardia, presumably by inhibiting serotonin-mediated vagal activation.[7–9]

Despite promising evidence, the efficacy of ondansetron for SAIH attenuation remains debated, with some studies reporting modest or no benefit, and considerable heterogeneity in study designs, dosing regimens, and outcome definitions.[10] Furthermore, the safety profile of ondansetron in pregnancy, particularly with respect to fetal outcomes, has been scrutinized, though large cohort studies and meta-analyses have not demonstrated increased risks of major congenital malformations or adverse perinatal events.[1–3]

Given these uncertainties, further real-world data from diverse clinical settings are needed to clarify the role of ondansetron in SAIH prevention.[11–13] This observational study was conducted at a large tertiary care teaching hospital in southern India to evaluate the effect of intravenous ondansetron on the incidence and severity of hypotension in parturients undergoing caesarean section under spinal anaesthesia.[11–13]Secondary objectives were assessment of intraoperative shivering, nausea, vomiting and rhythm disturbances; vasopressor requirements were also recorded.[1–3]

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted at the Department of Anaesthesiology and Critical Care, Justice K. S. Hegde Charitable Hospital, K. S. Hegde Medical Academy, NITTE (Deemed to be University), Deralakatte, Mangaluru, from 1 June 2023 to 30 November 2024. Convenience sampling was used.

Ethical Considerations

Institutional Ethics Committee approval was obtained before enrolment. Written informed consent was obtained from participants, and confidentiality was maintained.

Study Population

Inclusion Criteria

- Parturients aged 20–40 years
- Scheduled for caesarean section under spinal anaesthesia
- American Society of Anesthesiologists (ASA) physical status II

Exclusion Criteria

- Contraindications to spinal anaesthesia (e.g., coagulopathy, infection at puncture site)
- Patients taking selective serotonin reuptake inhibitors
- Patients allergic to ondansetron or local anaesthetics
- Patients with rhythm disturbances
- Refusal to participate

Exposure and Group Allocation

Participants were grouped according to prophylactic ondansetron exposure. Group O included 38 participants who received intravenous ondansetron 4 mg 10 minutes before spinal anaesthesia, and Group N included 38 participants who did not receive prophylactic ondansetron. The available description does not establish whether Group N received 2 mL normal saline or no prophylactic injection.

Anaesthetic Technique

All patients were preloaded with 500 mL Ringer's lactate according to the institutional protocol. Baseline SBP, DBP, MAP, HR and peripheral oxygen saturation were recorded before spinal anaesthesia.

Under aseptic precautions, spinal anaesthesia was performed in the lateral position at the L3–L4 interspace using a 23-gauge Quincke–Babcock needle and 10 mg (2 mL) of 0.5% hyperbaric bupivacaine. Patients were immediately positioned supine. The highest level of sensory blockade was recorded.

Intraoperative Management

SBP, DBP, MAP, HR and SpO_2 were recorded every 3 minutes for 30 minutes after spinal anaesthesia. Hypotension was defined as SBP below the lower of 90 mmHg and 80% of baseline SBP. Bradycardia was defined as HR below the lower of 50 bpm and 80% of baseline HR.

The study protocol specified intravenous ephedrine 6 mg for hypotension and intravenous atropine 0.6 mg for bradycardia. Intraoperative nausea, vomiting, shivering and rhythm disturbances, together with additional medications, were recorded.

Data Collection and Variables

Recorded variables included age, height, weight, BMI, baseline and serial haemodynamic measurements, SpO_2, highest sensory block level, ephedrine use and dose, duration of surgery, nausea and vomiting, shivering, rhythm disturbances and additional medications.

Sample Size and Power Calculation

The sample size was based on MAP at 6 minutes reported by Sahoo et al.: 87.5 ± 11.3 mmHg in the ondansetron group and 80.4 ± 10.8 mmHg in the saline group. The study specified 38 participants per group, totalling 76, with 95%

confidence and 80% power. This calculation was based on a between-group difference in MAP, rather than on hypotension incidence.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables were summarized as frequencies and percentages.

Between-group comparisons used independent-samples t-tests for normally distributed continuous data, Mann–Whitney U tests for skewed data, and chi-square tests for categorical variables. Repeated-measures ANOVA or the Friedman test was specified for comparisons across time points. The reported analysis does not identify which longitudinal test was performed, provide a group-by-time interaction result, or describe adjustment for multiple time-point comparisons.

RESULTS

Participant Flow and Baseline Characteristics

All 76 enrolled participants completed the study and were analysed, with 38 participants in Group O and 38 in Group N. No exclusions were reported among enrolled participants. Figure 1 summarises the reported enrolment, grouping and analysis.

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Group O (n=38)	Group N (n=38)	p-value
Age (years)	27.71 ± 4.90	28.13 ± 4.93	0.710
BMI (kg/m²)	26.36 ± 8.35*	25.25 ± 4.07	0.199
ASA II (%)	100	100	—
Baseline SBP (mmHg)	115.53 ± 7.24	114.47 ± 9.50	0.589
Baseline HR (bpm)	91.00 ± 8.15	92.37 ± 18.01	0.671

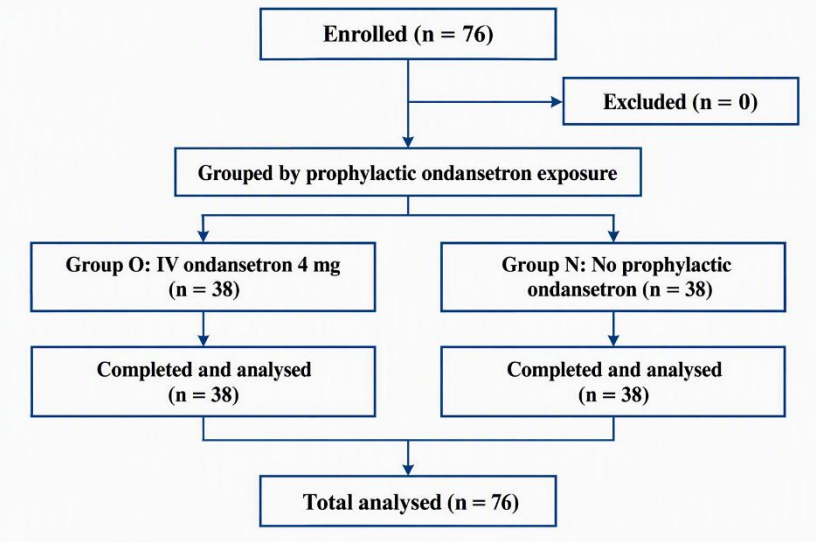


Figure 1. STROBE Participant Flow: Enrolled 76; Excluded 0; Group O 38; Group N 38; Analysed 76

Depicts screening, enrollment, allocation, follow-up, and analysis for both groups.

Incidence and Severity of Hypotension

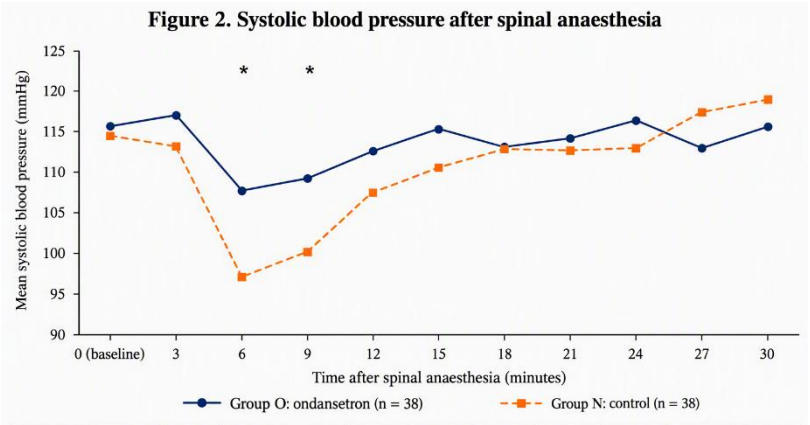
Group O had higher SBP at 6 minutes (107.65 ± 13.95 versus 97.10 ± 15.67 mmHg) and 9 minutes (109.08 ± 10.83 versus 100.13 ± 14.29 mmHg), with p=0.003 at each time point. MAP was also higher in Group O at 6, 9 and 12 minutes (p=0.001, 0.007 and 0.033, respectively). The reported hypotension counts were 11 participants in Group O and 28 in Group N. These counts remain unverified because the time-point narrative is internally inconsistent and may include repeated events; they therefore cannot yet be interpreted as patient-level incidence.

Table 2. Intraoperative Hemodynamic Outcomes and Vasopressor Use

Outcome	Group O (n=38)	Group N (n=38)	p-value
Hypotension	11	28	Not confirmed
Ephedrine use (%)	22/38 (57.9%)	32/38 (84.2%)	0.011
Nausea/vomiting (%)	2/38 (5.3%)	18/38 (47.4%)	<0.001

Outcome	Group O (n=38)	Group N (n=38)	p-value
Shivering (%)	5/38 (13.2%)	23/38 (60.5%)	<0.001

Ephedrine use, nausea and vomiting, and shivering were lower in Group O. No rhythm disturbances were reported in either group. Percentages are calculated from the reported counts and 38 participants per group; 22/38 rounds to 57.9%.



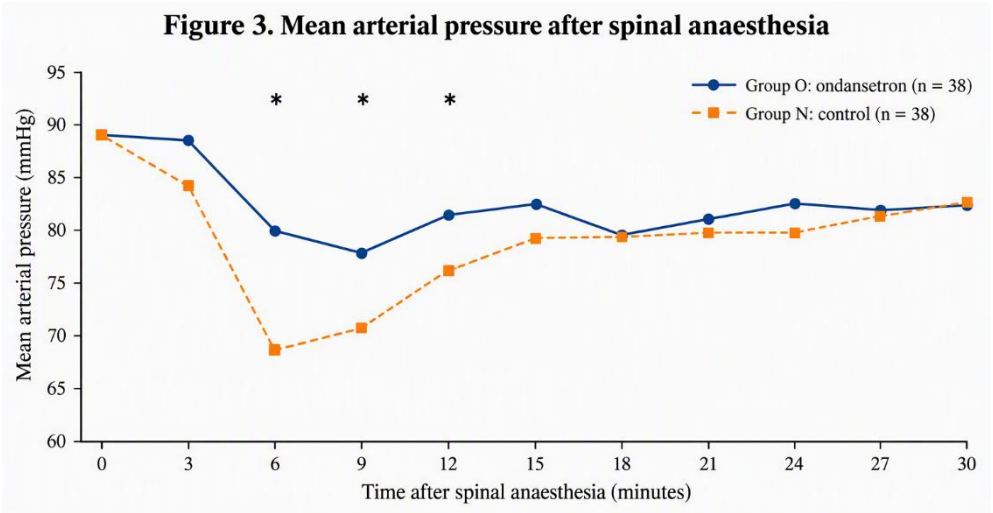
Time (min)	0 (baseline)	3	6	9	12	15	18	21	24	27	30
Group O	115.53	116.78	107.65	109.08	112.55	115.21	113.07	113.92	116.184	113.00	115.47
Group N	114.47	113.23	97.10	100.13	107.42	110.57	112.89	112.71	113.00	117.28	118.76

* Between-group $p = 0.003$ at 6 and 9 minutes.

Figure 2. Systolic Blood Pressure from Baseline to 30 Minutes after Spinal Anaesthesia

Serial Haemodynamic Measurements

SBP differed significantly between groups at 6 and 9 minutes, and DBP and MAP differed significantly at 6, 9 and 12 minutes. No significant between-group differences in HR or SpO_2 were reported during the 30-minute observation period. These findings describe selected time-point comparisons rather than a reported overall longitudinal treatment effect.



Time (minutes)	0	3	6	9	12	15	18	21	24	27	30
Group O (mmHg)	89.00	88.57	79.90	77.88	81.28	82.28	79.53	80.97	82.35	81.79	82.22
Group N (mmHg)	89.03	84.41	68.64	70.57	76.10	79.28	79.40	79.78	79.78	81.28	82.50

* Between-group p-values: 6 min = 0.001; 9 min = 0.007; 12 min = 0.033.

Figure 3. Mean Arterial Pressure from Baseline to 30 Minutes after Spinal Anaesthesia

Other Intraoperative Outcomes

Mean duration of surgery was 75.53 ± 7.78 minutes in Group O and 74.87 ± 12.91 minutes in Group N (p=0.789). Sensory block distributions did not differ significantly (p=0.141). Additional medications were used in 3/38 participants in Group O and 20/38 in Group N (p<0.001).

DISCUSSION

Principal Findings

In this prospective observational study of 76 participants, prophylactic intravenous ondansetron was associated with higher SBP at 6 and 9 minutes, higher DBP and MAP at 6, 9 and 12 minutes, and lower ephedrine use. Intraoperative nausea and vomiting and shivering were also less frequent in Group O. These are associations rather than proof of a causal treatment effect.

Comparison with Previous Literature

Our findings are consistent with several randomized controlled trials and meta-analyses that have reported a protective effect of ondansetron against SAIH in obstetric populations.[11–13] For example, a recent meta-analysis of 25 RCTs found that ondansetron reduced the risk of hypotension (RR 0.65, 95% CI 0.53–0.80) and bradycardia (RR 0.56, 95% CI 0.38–0.83), with a number needed to treat (NNT) of 7.5 for hypotension.[11–12] Another meta-analysis focusing on obstetric patients reported a relative risk of 0.53 (95% CI 0.32–0.86) for hypotension, with significant heterogeneity across studies.[11–12]

The mechanistic rationale for ondansetron's effect lies in its antagonism of 5-HT3 receptors on cardiac vagal afferents, thereby blunting the Bezold–Jarisch reflex—a key contributor to paradoxical bradycardia and vasodilation during acute reductions in ventricular filling following spinal anaesthesia.[7–9] By inhibiting this reflex, ondansetron may prevent inappropriate vagal activation and maintain vascular tone, resulting in improved hemodynamic stability.[7–9]

Interpretation should account for the observational design, convenience sampling and possible confounding. The study describes a standardised anaesthetic protocol but does not report adjusted regression or mixed-effects analyses. Similar baseline measurements do not by themselves eliminate confounding.

Dosing, Timing, and Safety Considerations

The study used a fixed intravenous ondansetron dose of 4 mg administered 10 minutes before spinal anaesthesia. Alternative doses and timing intervals were not compared, so this study cannot establish an optimal regimen.

No rhythm disturbances were reported among the 76 participants. This finding does not establish comprehensive maternal safety or neonatal safety. The study does not report study-level Apgar scores, umbilical artery pH or neonatal acidosis results.

Vasopressor Management and Comparison

The study reports ephedrine as the protocol vasopressor. Ephedrine was required in 22 participants in Group O and 32 in Group N (p=0.011). Its dose distribution was also lower in Group O, although the separate statistical test for dose distribution is not clearly documented. Mean phenylephrine requirements are not reported and cannot be presented as study findings.

Strengths and Limitations

Strengths include prospective observation, a standardised anaesthetic protocol, serial haemodynamic measurements, and assessment of intraoperative nausea, vomiting, shivering and medication requirements.

Limitations include the single-centre observational design, convenience sampling, 76-participant sample, fixed ondansetron dose and 30-minute haemodynamic observation period. Potential confounding was not resolved by reported adjusted analyses.

Implications for Practice and Future Research

The findings support further investigation of prophylactic ondansetron as an adjunct during spinal anaesthesia, rather than a definitive recommendation for routine use. Larger multicentre controlled studies, dose-response comparisons, longer follow-up and assessment of patient satisfaction are warranted.

CONCLUSION

Among 76 participants undergoing caesarean section under spinal anaesthesia, prophylactic intravenous ondansetron was associated with higher blood pressure at selected early time points, lower ephedrine requirements, and less intraoperative nausea, vomiting and shivering. The observational findings do not establish causality or neonatal safety. Reconciliation of the study's hypotension data and larger controlled studies are needed before definitive incidence or practice recommendations are made.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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