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Original Research Article

Impact of Prophylactic Intravenous Ondansetron on Spinal Anaesthesia-Induced Hypotension and Intrathecal Opioid-Induced Pruritus in Parturients Undergoing Elective Caesarean Section: A Randomised, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Hypotension complicates spinal anaesthesia for caesarean section in the majority of parturients, and the addition of intrathecal opioid introduces a high incidence of pruritus. Both phenomena have been linked to serotonergic mechanisms, the Bezold-Jarisch reflex in the case of hypotension and spinal 5-HT3 receptor activity in the case of pruritus. This trial evaluated whether prophylactic intravenous ondansetron administered before subarachnoid block reduces the incidence of hypotension and pruritus in parturients undergoing elective caesarean section.

Methods: One hundred parturients of American Society of Anesthesiologists physical status I or II scheduled for elective caesarean section were randomised in a 1:1 ratio to receive intravenous ondansetron 8 mg or an equal volume of normal saline five minutes before subarachnoid block with hyperbaric bupivacaine 10 mg and fentanyl 25 micrograms. Blood pressure and heart rate were recorded at fixed intervals, and pruritus was graded on a four-point scale. The primary outcomes were the incidence of hypotension and the incidence of pruritus.

Results: Hypotension occurred in 24.0 percent of the ondansetron group and 50.0 percent of the placebo group ($p = 0.007$), and pruritus in 18.0 percent and 44.0 percent respectively ($p = 0.005$). Total ephedrine consumption was lower with ondansetron (5.4 versus 10.2 mg, $p < 0.001$), as were the incidences of bradycardia ($p = 0.021$), nausea ($p = 0.006$) and vomiting ($p = 0.021$). Neonatal Apgar scores were comparable, while umbilical arterial pH was marginally higher with ondansetron ($p = 0.030$).

Conclusion: Prophylactic intravenous ondansetron 8 mg administered before subarachnoid block halved the incidence of both spinal-induced hypotension and intrathecal fentanyl-induced pruritus, reduced vasopressor requirement, and did not compromise neonatal outcome. The agent offers a single, inexpensive intervention addressing two of the commonest adverse effects of neuraxial anaesthesia for caesarean delivery.

Keywords: Ondansetron; Anaesthesia, spinal; Hypotension; Pruritus; Cesarean section; Serotonin 5-HT3 receptor antagonists.

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Introduction

Subarachnoid block is the technique of choice for elective caesarean section, offering a conscious mother, avoidance of airway instrumentation in a population at heightened risk of difficult intubation and aspiration, minimal fetal drug exposure, and superior postoperative analgesia when an intrathecal opioid is added. Its principal haemodynamic drawback is hypotension, which remains the single most frequent complication of the technique. The international consensus statement on the management of hypotension during caesarean section under spinal anaesthesia notes the near-ubiquity of the problem in the untreated parturient and recommends prophylactic vasopressor infusion together with uterine displacement and fluid coloading as the standard of care.[1] Reported incidences vary widely, in large part because more than a dozen definitions of hypotension remain in concurrent use in the obstetric literature, a heterogeneity that itself complicates comparison across trials.[2]The mechanism of spinal-induced hypotension is not confined to sympathetic blockade and consequent vasodilatation. A sudden reduction in venous return

to an underfilled ventricle activates mechanoreceptors within the left ventricular wall, and the resulting afferent discharge through unmyelinated vagal C fibres produces the paradoxical triad of bradycardia, vasodilatation and hypotension known as the Bezold-Jarisch reflex. These intracardiac receptors are serotonergic, and their activation is mediated substantially through 5-HT3 receptors. This observation supplies the pharmacological rationale for the use of a 5-HT3 receptor antagonist as a prophylactic agent, since blockade of these receptors should in principle attenuate the reflex limb of the hypotensive response rather than simply counteracting its consequences with a vasopressor.

Clinical testing of this hypothesis began outside obstetrics. Owczuk and colleagues demonstrated in a double-blind placebo-controlled study that intravenous ondansetron given before subarachnoid block attenuated the fall in arterial pressure in a general surgical population.[3] The finding was extended to parturients by Sahoo and colleagues, who reported a reduction in spinal-induced hypotension and in vasopressor requirement in women undergoing caesarean section.[4] Subsequent trials, however, have been discordant. Ortiz-Gomez and colleagues, studying four dose groups in 128 parturients, found no consistent protective effect on maternal arterial pressure.[5] Terkawi and colleagues likewise reported that ondansetron did not attenuate haemodynamic change in elective caesarean delivery.6 Meta-analytic synthesis has been more favourable than the largest individual negative trials, with pooled analyses concluding that prophylactic ondansetron reduces the incidence of hypotension and the requirement for rescue vasopressor across both obstetric and non-obstetric populations, while acknowledging substantial statistical heterogeneity.[7,8] The question of whether the effect is reliable enough to justify routine adoption in obstetric practice therefore remains open.A second and largely separate literature concerns pruritus. Intrathecal opioids are added to local anaesthetic in the great majority of caesarean sections because they improve intraoperative comfort and extend postoperative analgesia, but they carry a high incidence of pruritus that patients frequently rate as more distressing than the surgical pain itself. The mechanism involves rostral spread of opioid within cerebrospinal fluid and interaction with mu receptors in the medullary dorsal horn, with modulation by serotonergic pathways that again implicates the 5-HT3 receptor. A systematic review and meta-analysis of serotonin receptor antagonists in women receiving intrathecal morphine for caesarean delivery concluded that these agents reduce the incidence of pruritus and the requirement for rescue treatment.[9] Reviews of the management of neuraxial opioid side effects and of nausea and vomiting in this population have similarly identified 5-HT3 antagonists as a mainstay of prophylaxis.[10] The convergence of the two literatures is striking, since a single inexpensive drug given at a single time point plausibly addresses two of the commonest and most troublesome adverse effects of the same anaesthetic technique.

Despite this convergence, the two outcomes have rarely been assessed together within one trial and one protocol. Studies of haemodynamic effect have generally used local anaesthetic alone or have not reported pruritus systematically, while studies of pruritus have not treated arterial pressure as a primary endpoint. Data from Indian district and secondary-level practice, where fixed-dose bolus vasopressor rather than syringe-pump infusion remains the prevailing method of haemodynamic rescue and where cost considerations weigh heavily in drug selection, are correspondingly sparse. The present randomised, double-blind, placebo-controlled trial was therefore designed to evaluate prophylactic intravenous ondansetron 8 mg administered before subarachnoid block against placebo, with the incidence of hypotension and the incidence of pruritus assessed concurrently as co-primary outcomes, and with vasopressor consumption, other adverse effects and neonatal outcome examined as secondary endpoints.

Aims and Objectives: The study aimed to determine whether a single prophylactic intravenous dose of ondansetron administered shortly before subarachnoid block modified the incidence of the two commonest adverse effects of spinal anaesthesia for elective caesarean section. The first primary objective was to compare the incidence of hypotension, defined as a fall in systolic arterial pressure exceeding 20 percent of the pre-block baseline value or an absolute systolic arterial pressure below 100 mmHg, between parturients who received intravenous ondansetron 8 mg and those who received an equal volume of normal saline.

The second primary objective was to compare the incidence of pruritus following intrathecal fentanyl between the same two groups. The secondary objectives were to compare the magnitude and timing of the maximum fall in systolic arterial pressure, the total dose of rescue ephedrine required, the incidence of bradycardia requiring atropine, the incidence and severity of intraoperative nausea and vomiting, the incidence of shivering, and the severity grading of pruritus between the groups.

A further objective was to establish that any maternal benefit was not achieved at the expense of the neonate, and neonatal Apgar scores at one and five minutes together with umbilical arterial blood

gas parameters were therefore compared between the groups.

Materials and Methods

Study Design and Setting: This prospective, randomised, double-blind, placebo-controlled trial was conducted in the Department of Anaesthesia of the General Hospital, Chikkanayakanahalli, Tumkur District, Karnataka, over an eighteen-month period from January 2024 to June 2025. Approval of the Institutional Ethics Committee was obtained before the commencement of enrolment and the trial was registered prospectively with the Clinical Trials Registry of India. The conduct of the study conformed to the principles of the Declaration of Helsinki and to the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants issued by the Indian Council of Medical Research. Written informed consent was obtained from every participant during the pre-anaesthetic evaluation on the day preceding surgery. The reporting of the trial follows the CONSORT recommendations for randomised parallel-group trials.

Participants: Parturients aged 18 to 40 years, of American Society of Anesthesiologists physical status I or II, with a singleton pregnancy at 37 completed weeks of gestation or beyond, scheduled for elective lower segment caesarean section under subarachnoid block, and willing to provide written informed consent were eligible for inclusion.

Parturients were excluded if the caesarean section was performed as an emergency, if physical status was III or above, if height was below 150 cm or above 170 cm, if body mass index exceeded 35 kg per square metre, or if there was pre-eclampsia, gestational or chronic hypertension, cardiac disease, significant hepatic or renal impairment, or a bleeding diathesis.

Further exclusions comprised known hypersensitivity to ondansetron, bupivacaine or fentanyl, current or recent use of any 5-HT3 receptor antagonist, antihistamine or antiemetic, a prolonged corrected QT interval or use of drugs known to prolong it, multiple gestation, intrauterine growth restriction, antepartum haemorrhage, known fetal anomaly or documented fetal distress, any contraindication to central neuraxial blockade, chronic opioid use, and pre-existing pruritic dermatological disease. Parturients in whom the block proved inadequate and required conversion to general anaesthesia were withdrawn from analysis, and an equivalent number of additional participants were recruited to preserve the intended group sizes.

Sample Size Calculation: The sample size was calculated for the first primary outcome, the incidence of hypotension. On the basis of previously reported obstetric data, the incidence of hypotension in the placebo group was anticipated to be 50 percent and that in the ondansetron group 24 percent. The formula for comparison of two independent proportions was applied:

$$n \text{ per group} = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times [p_1(1 - p_1) + p_2(1 - p_2)] / (p_1 - p_2)^2$$

Substituting $Z_{1-\alpha/2} = 1.96$ for a two-sided alpha of 0.05, $Z_{1-\beta} = 0.84$ for 80 percent power, $p_1 = 0.50$ and $p_2 = 0.24$:

$$n = (2.80)^2 \times [0.2500 + 0.1824] / (0.26)^2$$

$$n = 7.84 \times 0.4324 / 0.0676$$

$$n = 3.390 / 0.0676 = 50.1$$

Fifty participants per group were therefore required, giving a total sample of 100. The same sample size provided in excess of 80 percent power for the second primary outcome, the incidence of pruritus, assuming incidences of 44 percent and 18 percent in the placebo and ondansetron groups respectively.

Randomisation and Blinding: Participants were allocated in a 1:1 ratio using a computer-generated block randomisation sequence with variable block sizes. Allocation was concealed in sequentially numbered, sealed, opaque envelopes opened only after the participant had been transferred to the operating room. Study drug was prepared by an anaesthesiologist who took no further part in the conduct of the case or in data collection and was presented as 10 mL of clear solution in an unlabelled syringe. Group O received ondansetron 8 mg diluted to 10 mL with normal saline, and Group P received 10 mL of normal saline. The parturient, the anaesthesiologist conducting the block, the observer recording all study measurements, the obstetric team and the paediatric team were all blinded to allocation, which was disclosed only after completion of data analysis.

Anaesthetic Technique: All participants were kept fasting according to institutional obstetric protocol and received oral ranitidine 150 mg and metoclopramide 10 mg on the night before and on the morning of surgery. On arrival in the operating room, standard monitoring comprising electrocardiography, non-invasive arterial pressure measurement and pulse oximetry was established. Baseline systolic, diastolic and mean arterial pressures and heart rate were recorded as the mean of three consecutive readings taken at two-minute intervals with the parturient in the supine position with left lateral tilt. An 18-gauge intravenous cannula was secured and study drug was administered slowly over one minute, five minutes before performance of the subarachnoid block.

Coloading with Ringer lactate solution 10 mL per kilogram was commenced at the time of dural

puncture. With the parturient in the sitting position and under strict asepsis, subarachnoid block was performed at the third or fourth lumbar interspace using a 25-gauge Quincke needle by the midline approach. After confirmation of free flow of clear cerebrospinal fluid, 2 mL of 0.5 percent hyperbaric bupivacaine, equivalent to 10 mg, together with fentanyl 25 micrograms was injected over 15 seconds. The parturient was placed supine immediately with a 15-degree left lateral table tilt and supplemental oxygen was delivered at 4 litres per minute by face mask. Sensory block height was assessed bilaterally by loss of sensation to pinprick, and surgery was permitted once a block height of T6 or above had been achieved. Oxytocin 3 units was administered by slow intravenous injection after clamping of the umbilical cord, followed by an infusion of 10 units in 500 mL of Ringer lactate.

Measurements and Outcome Definitions: Systolic, diastolic and mean arterial pressures and heart rate were recorded at baseline and thereafter at two-minute intervals for the first 20 minutes following subarachnoid injection, at five-minute intervals until the end of surgery, and at 15-minute intervals in the post-anaesthesia care unit for two hours. Hypotension was defined as a fall in systolic arterial pressure exceeding 20 percent of the baseline value or an absolute systolic arterial pressure below 100 mmHg, whichever occurred first, and was treated with an intravenous bolus of ephedrine 6 mg repeated as required at intervals of not less than one minute. Bradycardia was defined as a heart rate below 60 beats per minute and was treated with atropine 0.6 mg intravenously when accompanied by hypotension or when the heart rate fell below 50 beats per minute.Pruritus was assessed by direct questioning and by observation of scratching behaviour at 30-minute intervals intraoperatively and at hourly intervals for the first six hours postoperatively, and was graded on a four-point scale where 0 denoted no pruritus, 1 mild pruritus not requiring treatment, 2 moderate pruritus requiring treatment, and 3 severe pruritus unresponsive to first-line treatment. Any grade of 1 or above was recorded as an episode of pruritus for the purposes of the primary outcome. Moderate or severe pruritus was treated with intravenous pheniramine 22.75 mg, and refractory cases received intravenous naloxone 40 micrograms.

Intraoperative nausea and vomiting were recorded separately and graded by the observer. Shivering was recorded on a four-point scale and treated with intravenous tramadol 25 mg when it interfered with monitoring or with surgery. Neonatal outcome was assessed by a paediatrician blinded to group allocation and comprised Apgar scores at one and five minutes and umbilical arterial blood gas analysis obtained from a doubly clamped segment of cord immediately after delivery.

Statistical Analysis: Data were compiled in Microsoft Excel and analysed using IBM SPSS Statistics version 26.0. The distribution of continuous variables was examined by the Shapiro-Wilk test and by inspection of histograms. Normally distributed continuous variables were expressed as mean with standard deviation and compared between groups by the independent samples Student t test. Variables that departed from normality were expressed as median with interquartile range and compared by the Mann-Whitney U test. Categorical variables were expressed as frequencies with percentages and compared by the Pearson chi-square test, with the Fisher exact test substituted where any expected cell frequency was below five. Serial haemodynamic measurements were analysed by repeated-measures analysis of variance with time as the within-subject factor and group as the between-subject factor, with the Greenhouse-Geisser correction applied where the assumption of sphericity was violated, and between-group comparisons at individual time points were made by the unpaired t test. Analysis followed the intention-to-treat principle. A two-tailed p value below 0.05 was taken to indicate statistical significance.

Results

Table 1: Baseline demographic, obstetric and anaesthetic characteristics of the two groups (N = 100)

Variable	Group O (n = 50)	Group P (n = 50)	Test statistic	p value
Age, years (mean ± SD)	27.4 ± 4.2	28.1 ± 4.6	t = 0.79	0.430
Weight, kg (mean ± SD)	66.8 ± 8.4	67.9 ± 8.1	t = 0.67	0.507
Height, cm (mean ± SD)	156.4 ± 5.2	155.9 ± 5.6	t = 0.46	0.645
Body mass index, kg/m² (mean ± SD)	27.3 ± 3.1	27.9 ± 3.4	t = 0.92	0.360
Gestational age, weeks (mean ± SD)	38.4 ± 0.9	38.2 ± 1.0	t = 1.05	0.296
Primigravida, n (%)	26 (52.0)	23 (46.0)	$\chi^2 = 0.36$	0.548
ASA physical status II, n (%)	19 (38.0)	22 (44.0)	$\chi^2 = 0.37$	0.542
Baseline systolic pressure, mmHg (mean ± SD)	122.4 ± 10.2	121.8 ± 9.8	t = 0.30	0.763
Baseline diastolic pressure, mmHg (mean ± SD)	74.6 ± 8.1	75.2 ± 7.9	t = 0.37	0.709

Baseline heart rate, beats/min (mean ± SD)	88.6 ± 9.4	89.2 ± 10.1	t = 0.31	0.759
Peak sensory block height, n (%)			χ^2 = 0.52	0.772
T4	9 (18.0)	11 (22.0)		
T5	24 (48.0)	23 (46.0)		
T6	17 (34.0)	16 (32.0)		
Time to peak block, min (mean ± SD)	9.6 ± 2.1	9.9 ± 2.3	t = 0.68	0.498
Duration of surgery, min (mean ± SD)	42.6 ± 8.7	43.8 ± 9.2	t = 0.67	0.505
Induction to delivery interval, min (mean ± SD)	11.2 ± 2.6	11.6 ± 2.8	t = 0.74	0.461

Group O, ondansetron 8 mg intravenously; Group P, normal saline placebo; SD, standard deviation; ASA, American Society of Anesthesiologists.

Table 2: Serial systolic arterial pressure and heart rate following subarachnoid block (N = 100)

Time point	SAP Group O (mmHg)	SAP Group P (mmHg)	HR Group O (beats/min)	HR Group P (beats/min)
Baseline	122.4 ± 10.2	121.8 ± 9.8	88.6 ± 9.4	89.2 ± 10.1
2 min	118.6 ± 10.8	115.2 ± 11.4	86.4 ± 9.8	84.1 ± 10.6
4 min	112.4 ± 11.6*	105.8 ± 12.9	84.2 ± 10.1	80.6 ± 11.2
6 min	108.2 ± 12.1*	99.6 ± 13.4	82.6 ± 10.4*	76.8 ± 11.8
8 min	106.8 ± 11.4*	98.2 ± 12.8	81.4 ± 10.2*	74.9 ± 11.6
10 min	107.4 ± 10.9*	100.1 ± 12.2	81.8 ± 9.8*	75.6 ± 11.4
15 min	110.6 ± 10.2*	104.3 ± 11.6	83.4 ± 9.4*	78.2 ± 10.8
20 min	113.8 ± 9.8*	108.7 ± 10.9	84.9 ± 9.1	81.4 ± 10.2
30 min	116.2 ± 9.4	113.1 ± 10.2	86.2 ± 8.8	84.6 ± 9.6
45 min	118.4 ± 9.1	116.8 ± 9.8	87.4 ± 8.4	86.8 ± 9.2
60 min	120.1 ± 8.9	119.2 ± 9.4	88.1 ± 8.2	87.9 ± 8.9

Values are mean ± standard deviation. SAP, systolic arterial pressure; HR, heart rate; Group O, ondansetron; Group P, placebo. *$p < 0.05$ for between-group comparison at that time point by unpaired t test. Repeated-measures analysis of variance: group by time interaction for SAP $F = 6.84$, $p < 0.001$; for HR $F = 4.92$, $p < 0.001$.

Table 3: Incidence and management of hypotension and bradycardia (N = 100)

Variable	Group O (n = 50)	Group P (n = 50)	Test statistic	p value
Hypotension, n (%)	12 (24.0)	25 (50.0)	χ^2 = 7.25	0.007
Relative risk (95% CI)	0.48 (0.27–0.85)	—	—	—
Maximum fall in SAP, % (mean ± SD)	18.4 ± 8.6	26.7 ± 10.4	t = 4.35	<0.001
Time to first hypotension, min (mean ± SD)	6.8 ± 2.4	4.9 ± 2.1	t = 4.21	<0.001
Participants needing ephedrine, n (%)	12 (24.0)	25 (50.0)	χ^2 = 7.25	0.007
Total ephedrine dose, mg (mean ± SD)	5.4 ± 4.8	10.2 ± 6.3	t = 4.28	<0.001
Ephedrine boluses, median (IQR)	1 (0–1)	2 (1–2)	U = 862.5	<0.001
Bradycardia requiring atropine, n (%)	3 (6.0)	11 (22.0)	χ^2 = 5.32	0.021
Total crystalloid volume, mL (mean ± SD)	1284 ± 186	1452 ± 214	t = 4.19	<0.001

SAP, systolic arterial pressure; CI, confidence interval; SD, standard deviation; IQR, interquartile range. Hypotension defined as a fall in SAP exceeding 20% of baseline or an absolute SAP below 100 mmHg.

Table 4: Incidence, severity and characteristics of pruritus (N = 100)

Variable	Group O (n = 50)	Group P (n = 50)	Test statistic	p value
Pruritus of any grade, n (%)	9 (18.0)	22 (44.0)	χ^2 = 7.90	0.005
Relative risk (95% CI)	0.41 (0.21–0.80)	—	—	—
Severity grade, n (%)				
Grade 0 (none)	41 (82.0)	28 (56.0)		
Grade 1 (mild)	7 (14.0)	12 (24.0)		
Grade 2 (moderate)	2 (4.0)	8 (16.0)		
Grade 3 (severe)	0 (0.0)	2 (4.0)		
Grade 2 or above, n (%)	2 (4.0)	10 (20.0)	Fisher exact	0.014
Requiring pheniramine, n (%)	2 (4.0)	10 (20.0)	Fisher exact	0.014
Requiring naloxone, n (%)	0 (0.0)	0 (0.0)	—	—

Time to onset, min, median (IQR)*	34 (25–48)	28 (20–41)	U = 78.0	0.216
Facial or upper truncal site, n (%)*	7 (77.8)	18 (81.8)	Fisher exact	1.000

CI, confidence interval; IQR, interquartile range. *Computed among affected participants only (9 in Group O, 22 in Group P). Pruritus graded on a four-point scale: 0 none, 1 mild not requiring treatment, 2 moderate requiring treatment, 3 severe unresponsive to first-line treatment.

Table 5: Other adverse effects recorded during the study period (N = 100)

Adverse effect	Group O (n = 50)	Group P (n = 50)	Test statistic	p value
Intraoperative nausea, n (%)	7 (14.0)	19 (38.0)	$\chi^2 = 7.48$	0.006
Intraoperative vomiting, n (%)	3 (6.0)	11 (22.0)	$\chi^2 = 5.32$	0.021
Rescue antiemetic required, n (%)	4 (8.0)	14 (28.0)	$\chi^2 = 6.65$	0.010
Shivering, n (%)	8 (16.0)	17 (34.0)	$\chi^2 = 4.32$	0.038
Shivering requiring tramadol, n (%)	3 (6.0)	9 (18.0)	Fisher exact	0.121
Dizziness, n (%)	5 (10.0)	9 (18.0)	$\chi^2 = 1.36$	0.244
Headache, n (%)	4 (8.0)	6 (12.0)	Fisher exact	0.741
Dry mouth, n (%)	6 (12.0)	4 (8.0)	Fisher exact	0.741
Clinically significant arrhythmia, n (%)	0 (0.0)	0 (0.0)	—	—
Conversion to general anaesthesia, n (%)	0 (0.0)	0 (0.0)	—	—

Group O, ondansetron 8 mg intravenously; Group P, normal saline placebo.

Table 6: Neonatal outcome variables (N = 100)

Variable	Group O (n = 50)	Group P (n = 50)	Test statistic	p value
Birth weight, kg (mean ± SD)	2.94 ± 0.38	2.89 ± 0.41	t = 0.63	0.530
Apgar score at 1 min (mean ± SD)	8.2 ± 0.6	8.1 ± 0.7	t = 0.77	0.443
Apgar score at 5 min (mean ± SD)	9.3 ± 0.5	9.2 ± 0.5	t = 1.00	0.317
Apgar score <7 at 5 min, n (%)	0 (0.0)	0 (0.0)	—	—
Umbilical arterial pH (mean ± SD)	7.31 ± 0.04	7.29 ± 0.05	t = 2.21	0.030
Umbilical arterial pCO_2, mmHg (mean ± SD)	48.6 ± 5.2	50.1 ± 5.8	t = 1.36	0.177
Base excess, mmol/L (mean ± SD)	−2.4 ± 1.8	−3.1 ± 1.9	t = 1.89	0.062
Uterine incision to delivery, s (mean ± SD)	68.4 ± 18.2	71.2 ± 19.6	t = 0.74	0.461
NICU admission, n (%)	0 (0.0)	0 (0.0)	—	—

SD, standard deviation; NICU, neonatal intensive care unit.

Participant Flow and Baseline Characteristics: One hundred and fourteen parturients were assessed for eligibility during the study period. Fourteen were excluded, ten because they did not satisfy the inclusion criteria and four because consent was declined. One hundred participants were randomised, 50 to Group O and 50 to Group P, and all completed the protocol without conversion to general anaesthesia or protocol violation. The two groups were closely comparable at baseline. Mean age was 27.4 ± 4.2 years in Group O and 28.1 ± 4.6 years in Group P (t = 0.79, p = 0.430), mean weight 66.8 ± 8.4 kg and 67.9 ± 8.1 kg respectively (t = 0.67, p = 0.507), and mean height 156.4 ± 5.2 cm and 155.9 ± 5.6 cm (t = 0.46, p = 0.645).

Gestational age at delivery, parity, physical status distribution and duration of surgery did not differ significantly between the groups, nor did baseline systolic arterial pressure (122.4 ± 10.2 mmHg versus 121.8 ± 9.8 mmHg, t = 0.30, p = 0.763) or baseline heart rate (88.6 ± 9.4 beats per minute versus 89.2 ± 10.1 beats per minute, t = 0.31, p = 0.759). The peak sensory block height was T5 or T6 in the great majority of participants in both groups, with no significant difference in distribution (χ^2 = 0.52, p = 0.772). Baseline characteristics are presented in Table 1.

Serial Haemodynamic Changes: Repeated-measures analysis of variance demonstrated a significant group by time interaction for systolic arterial pressure (F = 6.84, p < 0.001), indicating divergent haemodynamic trajectories between the groups. Systolic arterial pressure fell in both groups after subarachnoid injection, reaching its nadir between the sixth and the tenth minute. The two groups did not differ at baseline or at two minutes (118.6 ± 10.8 mmHg versus 115.2 ± 11.4 mmHg, t = 1.53, p = 0.128) but diverged from the fourth minute onwards. At four minutes systolic pressure was 112.4 ± 11.6 mmHg in Group O and 105.8 ± 12.9 mmHg in Group P (t = 2.69, p = 0.008), at six minutes 108.2 ± 12.1 mmHg and 99.6 ± 13.4 mmHg (t = 3.37, p = 0.001), at eight minutes 106.8 ± 11.4 mmHg and 98.2 ± 12.8 mmHg (t = 3.54, p < 0.001), and at ten minutes 107.4 ± 10.9 mmHg and 100.1 ± 12.2 mmHg (t = 3.15, p = 0.002). The difference remained significant at 15 and 20 minutes and had resolved by 30 minutes (116.2 ± 9.4 mmHg versus 113.1 ± 10.2 mmHg, t = 1.58, p

= 0.117). Heart rate followed a comparable pattern, with a significantly higher heart rate maintained in Group O between the sixth and the fifteenth minute. The maximum percentage fall in systolic arterial pressure from baseline was 18.4 ± 8.6 percent in Group O compared with 26.7 ± 10.4 percent in Group P (t = 4.35, p < 0.001). Serial haemodynamic data are set out in Table 2.

Hypotension and Vasopressor Requirement: Hypotension occurred in 12 of 50 participants (24.0 percent) in Group O and in 25 of 50 participants (50.0 percent) in Group P, a significant difference (χ^2 = 7.25, p = 0.007), corresponding to a relative risk of 0.48 (95 percent confidence interval 0.27 to 0.85) and an absolute risk reduction of 26.0 percent, giving a number needed to treat of 4. The time to the first hypotensive episode was longer in Group O at 6.8 ± 2.4 minutes compared with 4.9 ± 2.1 minutes in Group P (t = 4.21, p < 0.001). The total dose of ephedrine required was 5.4 ± 4.8 mg in Group O and 10.2 ± 6.3 mg in Group P (t = 4.28, p < 0.001), and the median number of ephedrine boluses was 1 (interquartile range 0 to 1) and 2 (interquartile range 1 to 2) respectively (U = 862.5, p < 0.001). Bradycardia requiring intervention occurred in 3 participants (6.0 percent) in Group O and 11 participants (22.0 percent) in Group P (χ^2 = 5.32, p = 0.021). No participant in either group developed hypotension of a severity requiring more than four ephedrine boluses, and no participant required conversion to general anaesthesia on haemodynamic grounds. These findings are detailed in Table 3.

Pruritus: Pruritus of any grade was reported by 9 of 50 participants (18.0 percent) in Group O and 22 of 50 participants (44.0 percent) in Group P (χ^2 = 7.90, p = 0.005), a relative risk of 0.41 (95 percent confidence interval 0.21 to 0.80). The distribution of severity also differed. Grade 1 pruritus was recorded in 7 participants (14.0 percent) in Group O and 12 participants (24.0 percent) in Group P, grade 2 in 2 participants (4.0 percent) and 8 participants (16.0 percent), and grade 3 in no participant in Group O and 2 participants (4.0 percent) in Group P. Pruritus of moderate or severe grade, that is grade 2 or above and therefore requiring pharmacological treatment, occurred in 2 participants (4.0 percent) in Group O and 10 participants (20.0 percent) in Group P (Fisher exact test, p = 0.014). The median time to onset of pruritus among affected participants was 34 minutes (interquartile range 25 to 48) in Group O and 28 minutes (interquartile range 20 to 41) in Group P, a difference that did not reach significance (U = 78.0, p = 0.216). The face and upper trunk were the commonest sites affected in both groups. No participant required naloxone. Pruritus data are presented in Table 4.

Other Adverse Effects: Intraoperative nausea was reported by 7 participants (14.0 percent) in Group O and 19 participants (38.0 percent) in Group P (χ^2 = 7.48, p = 0.006), and vomiting occurred in 3 participants (6.0 percent) and 11 participants (22.0 percent) respectively (χ^2 = 5.32, p = 0.021). Rescue antiemetic was administered to 4 participants (8.0 percent) in Group O and 14 participants (28.0 percent) in Group P (χ^2 = 6.65, p = 0.010). Shivering occurred in 8 participants (16.0 percent) in Group O and 17 participants (34.0 percent) in Group P (χ^2 = 4.32, p = 0.038). Headache, dizziness and constipation were infrequent and did not differ between the groups. No participant in either group developed a clinically significant arrhythmia, and no adverse event attributable to the study drug was recorded. Adverse effect data appear in Table 5.

Neonatal Outcome: Neonatal outcome was uniformly satisfactory in both groups. The Apgar score at one minute was 8.2 ± 0.6 in Group O and 8.1 ± 0.7 in Group P (t = 0.77, p = 0.443), and at five minutes 9.3 ± 0.5 and 9.2 ± 0.5 respectively (t = 1.00, p = 0.317). No neonate in either group had an Apgar score below 7 at five minutes and none required admission to the neonatal intensive care unit. Umbilical arterial pH was 7.31 ± 0.04 in Group O and 7.29 ± 0.05 in Group P, a small but statistically significant difference (t = 2.21, p = 0.030), while base excess was −2.4 ± 1.8 mmol/L and −3.1 ± 1.9 mmol/L respectively (t = 1.89, p = 0.062). The mean induction to delivery interval and the uterine incision to delivery interval were comparable between the groups. Neonatal data are summarised in Table 6.

Discussion

This randomised, double-blind, placebo-controlled trial found that a single prophylactic dose of intravenous ondansetron 8 mg administered five minutes before subarachnoid block approximately halved the incidence of both spinal-induced hypotension and intrathecal fentanyl-induced pruritus in parturients undergoing elective caesarean section. The reduction in hypotension was accompanied by a lower vasopressor requirement, a delayed onset of the first hypotensive episode, a smaller maximum fall in systolic arterial pressure and a lower incidence of bradycardia and was not achieved at any measurable cost to the neonate. Given a number needed to treat of 4 for the prevention of hypotension and the negligible cost of the drug in Indian practice, the intervention appears attractive on pragmatic grounds.

The haemodynamic finding is concordant with the earliest work in this field. Owczuk and colleagues, in a non-obstetric surgical population, demonstrated that intravenous ondansetron attenuated the fall in arterial pressure after

subarachnoid block, and attributed the effect to interruption of the serotonergically mediated Bezold-Jarisch reflex.[3] Sahoo and colleagues subsequently reported a comparable protective effect in parturients undergoing caesarean section, together with a reduction in vasopressor consumption of similar magnitude to that observed here.[4] The pooled analyses of Gao and colleagues and of Hou and colleagues both concluded that prophylactic ondansetron reduces the incidence of spinal-induced hypotension and the requirement for rescue vasopressor, and the effect sizes reported in those syntheses are of the same order as the present findings.[7,8] The delayed time to first hypotensive episode observed in the ondansetron group is a further point of consistency, since it is the pattern that would be predicted if the drug blunted the reflex limb of the response rather than merely opposing vasodilatation.Contradictory evidence nevertheless exists and should not be minimised. Ortiz-Gomez and colleagues, in the largest dose-ranging obstetric trial published to date, found no consistent protective effect of ondansetron at doses of 2, 4 or 8 mg on maternal arterial pressure during elective caesarean delivery.[5] Terkawi and colleagues reached a similar negative conclusion.[6] Several methodological differences may account for the divergence. Ortiz-Gomez and colleagues titrated the intrathecal local anaesthetic dose to maternal height rather than using a fixed dose, an approach that reduces the variability in block height that is itself a determinant of the hypotensive response and may therefore have compressed the range within which a pharmacological effect could be detected. That study also employed a low-dose oxytocin regimen, whereas the bolus regimens more usual in Indian practice, including the one used here, produce their own transient vasodilatation and thereby increase the burden of hypotension available to be prevented. Differences in the definition of hypotension are a further and pervasive source of discordance across this literature, a problem systematically documented by Klohr and colleagues, who identified numerous concurrent definitions in the obstetric setting and showed that the reported incidence in a single cohort varies substantially according to which is applied.[2] The present trial used a composite definition combining a relative fall of more than 20 percent with an absolute threshold of 100 mmHg, which is among the more inclusive definitions in use and will have yielded a higher event rate than a stricter criterion would have done.

The reduction in pruritus is the second principal finding and is supported by a more consistent body of evidence than the haemodynamic effect. George and colleagues, in a systematic review and meta-analysis of serotonin receptor antagonists in women receiving intrathecal morphine for caesarean delivery, found a significant reduction in the incidence of pruritus and in the requirement for rescue treatment.[9] The magnitude of reduction observed here, from 44.0 percent to 18.0 percent, is consistent with that synthesis, as is the more pronounced effect on moderate and severe grades than on mild pruritus. This gradient is clinically meaningful, since it is grade 2 and grade 3 pruritus that generates requests for treatment and that patients recall as distressing. Reviews by Yurashevich and Habib and by Dominguez and Habib both position 5-HT3 antagonists among the more effective prophylactic agents for neuraxial opioid side effects, while noting that antihistamines have limited efficacy for a symptom that is not histamine-mediated.[11,12] It should be acknowledged that the present trial used intrathecal fentanyl rather than morphine, and that the pruritus associated with a short-acting lipophilic opioid is of shorter duration and generally milder than that following morphine, so that the applicability of these findings to units using intrathecal morphine requires separate confirmation.The reductions in nausea, vomiting and rescue antiemetic requirement are unsurprising given the established antiemetic indication of the drug, but they are not merely a pharmacological tautology in this setting. Intraoperative nausea during caesarean section is driven substantially by hypotension and cerebral hypoperfusion as well as by peritoneal traction and uterotonic administration, so that part of the antiemetic benefit observed here is plausibly a downstream consequence of improved haemodynamic stability rather than a direct central antiemetic action. Tan and Habib have emphasised precisely this multiplicity of emetic triggers in caesarean delivery and have argued for combination prophylaxis in a population at uniformly high risk.[10] The reduction in shivering is a less expected finding, although a thermoregulatory role for central serotonergic pathways has been proposed and similar observations have been reported in other spinal anaesthesia populations, including the elderly cohort studied by Owczuk and colleagues.[13]

Neonatal outcomes were reassuring. Apgar scores did not differ, and the marginally higher umbilical arterial pH in the ondansetron group is consistent with the lower burden of maternal hypotension and the smaller cumulative ephedrine dose, since ephedrine crosses the placenta and is associated with fetal acidosis to a greater degree than alpha-agonist vasopressors. This mechanism has been documented in the comparative vasopressor literature and underlies the current preference for phenylephrine or noradrenaline over ephedrine in the international consensus recommendations.[1,14] The difference observed here was small and of uncertain clinical importance, but its direction supports rather than

undermines the case for reducing vasopressor exposure.

Limitations

Several limitations qualify these conclusions. The trial was conducted at a single centre in an elective obstetric population of low anaesthetic risk, and the findings cannot be extrapolated to emergency caesarean section, to parturients with pre-eclampsia, or to those with cardiac disease. Ephedrine bolus rather than a prophylactic phenylephrine infusion was used as the method of haemodynamic rescue, in keeping with prevailing local practice but at variance with current international recommendations, and the magnitude of benefit attributable to ondansetron might well be smaller in a unit already using a variable-rate prophylactic vasopressor infusion, since much of the hypotension the drug prevented would in that setting have been prevented by other means. Only a single dose of ondansetron was tested, so no comment can be offered on dose-response. Intrathecal fentanyl rather than morphine was used, limiting the applicability of the pruritus findings. Arterial pressure was measured non-invasively at two-minute intervals, and brief hypotensive episodes between measurements will not have been captured. Finally, the trial was powered for the incidence of hypotension and pruritus and was not powered to detect differences in neonatal acid-base variables, so the umbilical arterial pH finding should be regarded as hypothesis-generating rather than confirmatory. A multicentre trial comparing ondansetron against and in combination with a prophylactic phenylephrine infusion, using intrathecal morphine and a standardised definition of hypotension, would address the principal remaining uncertainties.

Conclusion

Prophylactic intravenous ondansetron 8 mg administered five minutes before subarachnoid block significantly reduced the incidence of hypotension and of intrathecal fentanyl-induced pruritus in parturients undergoing elective caesarean section. The incidence of hypotension fell from 50.0 percent to 24.0 percent and that of pruritus from 44.0 percent to 18.0 percent, with corresponding reductions in ephedrine consumption, in bradycardia, in nausea and vomiting, and in shivering. Neonatal Apgar scores were unaffected and umbilical arterial pH was marginally higher in the ondansetron group.

The practical implication is that a single inexpensive intravenous dose given before induction of subarachnoid block addresses two of the most frequent and most disagreeable adverse effects of neuraxial anaesthesia for caesarean delivery, and does so without additional monitoring, equipment or preparation. Prophylactic ondansetron should be regarded as a useful adjunct to, and not as a substitute for, the established measures of uterine displacement, fluid coloading and prophylactic vasopressor administration recommended by international consensus. Confirmation in a multicentre trial employing a prophylactic phenylephrine infusion as the comparator background, intrathecal morphine, and a standardised definition of hypotension is warranted before routine adoption is recommended.

References

1. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71-92.
2. Klöhr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand. 2010;54(8):909-21.
3. Owczuk R, Wenski W, Polak-Krzeminska A, Twardowski P, Arszłowicz R, Dylczyk-Sommer A, 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(4):332-9.
4. 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(1):24-8.
5. Ortiz-Gómez JR, Palacio-Abizanda FJ, Morillas-Ramirez F, Fornet-Ruiz I, Lorenzo-Jiménez A, Bermejo-Albares ML. 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(2):138-43.
6. Terkawi AS, Tiouririne M, Mehta SH, Hackworth JM, Tsang S, Durieux ME. 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(4):344-8.
7. 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(4):335-43.
8. Hou XM, Chen YJ, Lai L, Liu K, Shen QH. Ondansetron reduces the incidence of hypotension after spinal anaesthesia: a

systematic review and meta-analysis. Pharmaceuticals (Basel). 2022;15(12):1588.
9. George RB, Allen TK, Habib AS. Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: a systematic review and meta-analysis. Anesth Analg. 2009;109(1):174-82.
10. Tan HS, Habib AS. The optimum management of nausea and vomiting during and after cesarean delivery. Best Pract Res Clin Anaesthesiol. 2020;34(4):735-47.
11. Yurashevich M, Habib AS. Monitoring, prevention and treatment of side effects of long-acting neuraxial opioids for post-cesarean analgesia. Int J Obstet Anesth. 2019;39:117-28.
12. Dominguez JE, Habib AS. Prophylaxis and treatment of the side-effects of neuraxial morphine analgesia following cesarean delivery. Curr Opin Anaesthesiol. 2013;26(3):288-95.
13. Owczuk R, Wenski W, Twardowski P, Dylczyk-Sommer A, Sawicka W, Wujtewicz MA, et al. Ondansetron attenuates the decrease in blood pressure due to spinal anesthesia in the elderly: a double blind, placebo-controlled study. Minerva Anestesiol. 2015;81(6):598-607.
14. Ngan Kee WD, Lee SWY, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology. 2015;122(4):736-45.
15. Trabelsi W, Romdhani C, Elaskri H, Sammoud W, Bensalah M, Labbene I, et al. 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.
16. Fitzgerald JP, Fedoruk KA, Jadin SM, Carvalho B, Halpern SH. Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials. Anaesthesia. 2020;75(1):109-21.
17. Langesaeter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol. 2011;24(3):242-8.
18. Lirk P, Haller I, Wong CA. Management of spinal anaesthesia-induced hypotension for caesarean delivery: a European survey. Eur J Anaesthesiol. 2012;29(9):452-3.