INTRODUCTION

Spinal anesthesia is the technique of choice for caesarean sections (CSs). Hypotension associated with this technique potentially contributes to adverse maternal and foetal outcomes. Various pharmacological and non-pharmacological techniques have been employed to avoid or minimise hypotension. Fluid preloading/co-loading, vaspressors, compressive stockings, and acupressure have been employed with varying degrees of success. Recently, ondansetron and glycopyrrolate have been shown to minimise vasopressor requirements. Whether a combination of these drugs is effective in the real-world scenario is not sufficiently studied. We hypothesised that a combination of these drugs might be effective in minimising hypotension. The aim of this pragmatic study was to analyse the

Effect of prophylactic combination of glycopyrrolate, ondansetron, and ephedrine upon hypotension during obstetric spinal anaesthesia-A randomised controlled trial

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ABSTRACT

Background and Aims: Various pharmacological and non-pharmacological strategies have been employed to minimise hypotension during obstetric spinal anaesthesia. We compared a prophylactic combination of glycopyrrolate, ondansetron, and ephedrine in terms of total vasopressor consumption, with standard treatment in this randomised controlled trial. Methods: One hundred patients undergoing elective caesarean sections were randomly divided into two groups of 50 each, the study group received prophylactic ondansetron and glycopyrrolate boluses followed by an infusion of ephedrine, while the control group received ephedrine boluses as required. The total ephedrine consumption (primary objective), incidence and degree of hypotension, heart rate variations, and neonatal APGAR scores (secondary objectives) were analysed. Results: The median ephedrine requirement was lesser in the study group compared to the control group [13.2 mg (10–15.75) vs. 27.7 mg (12–24)], with a P value of 0.02. Fewer participants experienced hypotension in the study group before baby delivery compared to the control group (12 vs. 36, P = 0.004). Heart rate was higher in the study group. No significant differences were observed in neonatal APGAR scores and incidence of adverse events. Conclusion: A combination of glycopyrrolate, ondansetron, and ephedrine might offer better haemodynamic stability and reduce vasopressor consumption in obstetric patients undergoing spinal anaesthesia as opposed to standard treatment.

Key words: Anaesthesia spinal, caesarean section, ephedrine, glycopyrrolate, hypotension, ondansetron

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effect of a prophylactic combination of ondansetron, glycopyrrolate, and ephedrine upon post-spinal hypotension in obstetric patients in terms of total vasopressor consumption (primary objective). The secondary objectives were incidence and degree of hypotension, heart rate variations, adverse events, and neonatal APGAR scores.

METHODS

After obtaining Institutional ethics committee approval, the trial was registered with the Clinical Trials Registry-India (CTRI/2020/11/028792). The trial was conducted between November 2020 and July 2021 in a teaching hospital. One hundred consecutive parturients scheduled for elective CS were recruited. Informed written consent was obtained from all participants. The inclusion criterion was parturients aged 18–35 years with singleton pregnancy scheduled to undergo elective CS (category 3 and 4) under spinal anaesthesia. Exclusion criteria were the presence of comorbid conditions (cardiovascular, respiratory, neurological), contraindications to spinal anaesthesia, pregnancy-induced hypertension, multiple gestations, and abnormal placentation. Using computer-generated randomisation tables, the study participants were randomised into two groups of 50 each in blocks of five. The participants, anaesthesiologists administering the drugs and assessing outcomes were blinded to the group allocation. Sealed opaque envelopes were used to conceal group allocation.

All participants received oral ranitidine 150 mg and metoclopramide 10 mg the night before and were fasting overnight. Clear liquids were allowed till 2 h before surgery. In the operation theatre, standard monitors (3 lead electrocardiogram, non-invasive blood pressure, pulse oximetry) were attached and baseline parameters [heart rate, systolic and diastolic blood pressures, peripheral oxygen saturation (Spo2)] were recorded. The 90% values of baseline systolic blood pressure (SBP) were calculated to serve as threshold values for defining hypotension.

The study group received a single intravenous bolus each of glycopyrrolate 0.2 mg and ondansetron 4 mg before positioning for spinal anaesthesia. In the left lateral position, spinal anaesthesia was administered with 2 ml of 0.5% bupivacaine heavy and 30 µg buprenorphine in L3L4/L4L5 interspace using a 25G Quincke type spinal needle (BD Medical, NJ, USA) using standard technique. Co-loading was done with ringer lactate 20 ml/kg. An infusion of ephedrine 10 mg in 100 ml normal saline (NS) was started via a separate intravenous line at a rate of 10 ml/min. using an infusion pump while the spinal anaesthetic was being injected. The control group received normal saline placebo in lieu of glycopyrrolate and ondansetron injections. Spinal anaesthesia and fluid co-loading were performed similarly followed by a placebo 100 ml NS infusion which was started during intrathecal drug administration. All injections and infusions were prepared by an anaesthesiologist not involved in the patient management. A wedge was applied to provide a 15° left lateral tilt. Vitals were monitored at baseline and every minute thereafter till baby delivery beyond which 3-min. cycles were used. The sensory level was judged by hypoaesthesia to pinprick after positioning and every minute till a minimum level of T6 was achieved.

Hypotension – defined as a SBP of less than 90% of baseline value was treated with ephedrine bolus 6 mg, and bradycardia (defined as a heart rate less than 60) was treated with atropine 0.6 mg. After baby delivery, hypotension was defined as a fall in SBP of more than 30% of the baseline value and treated in the same manner. The primary objective of the study was total intraoperative ephedrine required, while secondary objectives were the number of episodes of hypotension before baby delivery, neonatal APGAR scores at 0 and 3 min, maximum sensory level, baby delivery time, total intravenous fluids, oxytocin doses, and any adverse events.

The sample size was calculated with a superiority design to detect a 30% mean difference in vasopressor consumption, two-sided significance, power of 80, alpha value of 0.05, 1:1 allocation ratio, and standard deviation of 6.33 (obtained from a previous study measuring ephedrine requirements in obstetric patients).[2] A sample size of 90 was obtained. Accounting for dropouts, a sample size of 100 was chosen.

Shapiro-Wilk test was used to test the normal distribution of data. Parametric data (heart rate, blood pressure) were analysed using unpaired Student’s t-test and non-parametric data using Mann–Whitney U test. For the incidence of hypotension at various time intervals, Kaplan-Meier survival analysis was done. Categorical data were analysed using Chi-square test/Fisher’s exact test as applicable. A P value less than 0.05 was considered significant. Parametric data were expressed as mean ± standard deviation (SD),
non-parametric data as mean and interquartile range (IQR). Statistics were performed using Microsoft Excel 2016 with Real statistics add-in package.

**RESULTS**

All participants completed the study [Figure 1]. The age, body mass index (BMI), baseline haemodynamic parameters, mean sensory level, and induction to baby delivery time were comparable in both groups [Table 1].

The mean ephedrine consumption was significantly lower in the study group compared to the control group [13.2 mg (10—15.75) vs. 27.7 mg (12--24); \( P = 0.026 \)] [Table 1].

Out of 50 patients in each group, 12 patients in the study group had at least one episode of hypotension before baby delivery, whereas 36 patients experienced hypotension in the control group. The maximum induction to baby delivery time was 15 min. The mean SBP of the study group patients was higher than the 90% threshold at all time points till 15 min. Such an observation was not seen in the control group [\( P = 0.02 \), Table 2].

Between-group comparisons revealed comparable mean SBP values in both groups and significantly lower mean DBP values in the control group at 3 min and 18 min, comparable at all other time intervals [Figure 2]. The heart rate was higher in the study group compared to control at all time points, but did not achieve statistical significance. SBP values were comparable in both groups at all time points [Table 2].

Within-group comparison revealed several significant findings. Statistically significant hypotension was observed in the control group at all time points when

| Parameter                  | Study     | Control   | \( P \) |
|----------------------------|-----------|-----------|---------|
| Age (years, mean±SD)       | 28.8±3.6  | 27.5±4.4  | 0.42    |
| BMI (kg/m\(^2\), mean±SD)  | 31.1±5.2  | 33.9±3.27 | 0.27    |
| Sensory level (mean, range) | T6 (4-6)  | T6 (4-7)  | 0.14    |
| Baby delivery time (minutes, mean±SD) | 11.69±2.71 | 10.3±1.8 |         |
| Ephedrine (mg, mean±SD)    | 13.16±2.8 | 27.72±6.98| 0.026   |
| Hypotensive episodes \( n \) | 12        | 36        | 0.004   |
| APGAR 0 min                | 8         | 8         |         |
| 3 min                      | 9         | 9         |         |

BMI – Body Mass Index; SD – Standard Deviation Age, BMI. Delivery times—unpaired \( t \) test. Ephedrine dose, hypotensive episodes —Mann Whitney \( U \) test

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**Figure 1:** CONSORT diagram
compared to the baseline [Table 2]. The maximum fall was at 9 min after induction. In the study group, significant hypotension was observed during 15 and 18 min after induction. The maximum fall was observed at 27 min [Figure 2] well beyond the baby delivery time (11.6 ± 2.7 min).

The Kaplan–Meier survival analysis survival probability score was significantly better in the study group than the control group. The proportion of patients remaining without hypotension was higher in the study group than control at all time points [Figure 3]. Among the patients who experienced hypotension, the degree of hypotension was comparable in both groups till baby delivery [Mean 8.83 (2.8–12) vs. 8.5 (2.5–18) mmHg, study and control respectively]. Two patients in the control group complained of nausea, none in the study group. The total intravenous fluids and oxytocin doses were similar in both groups. The neonatal APGAR scores were similar in both groups and no adverse events were observed.

**DISCUSSION**

We have evaluated a combination of three drugs that act by three different mechanisms for avoiding hypotension, perhaps for the first time. A significant decrease in ephedrine consumption has been demonstrated in our study group compared to controls. Fewer patients (12/50) had episodes of hypotension in the study group compared to the control group.

In a real-world scenario, avoiding hypotension may be more important rather than treating it, hence the popularity of prophylactic vasopressor infusions. Hypotension following spinal anaesthesia seems unavoidable in obstetric patients. To date, no technique has been shown to reliably avoid hypotension in all parturients. The mechanism of hypotension is multifactorial-arteriolar dilatation and decrease in systemic vascular resistance being predominant, hence vasopressors are the mainstay of treatment. Other factors like aortocaval compression,
intravascular volume redistribution, decrease in cardiac output may not contribute significantly, as strategies addressing them alone have not shown to be effective in preventing hypotension. A genetic basis for propensity to hypotension has also been proposed. Recently, ondansetron has been shown to minimise the incidence of hypotension and bradycardia by inhibiting the Bezold–Jarisch reflex. The effect was only moderate (NNT of 5.3 and 7.6 for preventing hypotension and bradycardia). A dose of 4 mg seems ideal. It may not be effective in all parturients and the results are not uniform. Anticholinergic drugs also can decrease vasopressor requirement, but may not reduce the incidence of hypotension. The effect may be modest and associated with higher heart rates.

We have used on-demand boluses of ephedrine as control rather than an infusion regimen, as this is the conventional approach followed in our practice. The long undisputed position of phenylephrine as the vasopressor of choice has been challenged by alternatives like noradrenaline and metaraminol. Compared to phenylephrine, ephedrine is cheaper, easier to prepare for administration, and widely available in our setup. A recent Cochrane review suggests no clear difference between them with respect to hypotension prevention, vomiting, and neonatal acidosis. Also, bradycardia is less common with ephedrine. Ephedrine boluses appear to be equivalent to phenylephrine even in potential foetal compromise. Hence, ephedrine was used as a vasopressor in the current study.

A threshold of 90% of baseline SBP value was used to define hypotension till baby delivery in the present study, as recent evidence suggests better outcomes with this approach. This might explain the slightly higher ephedrine requirements in the control group when compared to older studies which have used a 90 mmHg SBP as the cut-off value and closer to recent studies which have used an 80% baseline to define hypotension. Throughout the intraoperative period, the overall incidence of hypotension in the study group was 60% versus 90% in the control group. The timing of the onset of hypotension varied conspicuously. While it occurred much earlier in the control group, it was much later in the study group (mean time of maximum hypotension was 27 min in the study group versus 9 min in the control group). Kaplan–Meier survival estimates demonstrate this effect, where the study group had a higher proportion of patients not experiencing hypotension at all measured time points compared to controls. The increased heart rate seen in the study group can be attributed to both ephedrine and glycopyrrolate. Severe tachycardia warranting intervention is unusual with these drugs and the maximum average heart rate increase observed in our study was 14 beats per minute over the baseline (mean 10, range 5–14) and it resolved without intervention. It must be noted that this tachycardia might be undesirable in certain patient categories.

The main strength of the current study is its pragmatic nature – instead of focusing on the contribution of individual drugs, we have used a combination of them and assessed its overall effect compared to the conventional approach of administering on-demand vasopressor boluses. The individual contribution of the study drugs towards this objective might be apparent by multiple arm trials. We have chosen a threshold of 90% to define hypotension in line with recent recommendations. The timing and severity of hypotension were also analysed, offering useful insights. The study has some limitations. The umbilical cord pH was not analysed due to cost constraints. Conventional non-invasive blood pressure measurements were used, which might be less accurate than intra-arterial pressures. Ephedrine rather than phenylephrine or noradrenaline was used as the primary vasopressor, yet the most effective agent is still a question of research.

### CONCLUSION

In conclusion, a prophylactic combination of glycopyrrolate, ondansetron, and ephedrine offers better haemodynamic stability in terms of total vasopressor consumption, incidence, and severity of hypotension compared to on-demand ephedrine boluses.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.
Conflicts of interest

There are no conflicts of interest.

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