Original Article

Efficacy of fixed-dose phenylephrine bolus for treating post-spinal hypotension: Comparison between pre-eclamptics and normotensives

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Abstract

Background and Aims: Pre-eclamptic parturients may have an exaggerated response to vasopressors. This study compares the efficacy of a 50 μg fixed bolus of phenylephrine for treatment of post-spinal hypotension in pre-eclamptic versus normotensive parturients.

Material and Methods: After written informed consent and ethics committee approval, 30 normotensive and 30 pre-eclamptic parturients between 18 and 40 years with singleton term pregnancy about to undergo cesarean section (CS) under spinal anesthesia were included. Post-spinal hypotension was treated with a 50 μg fixed bolus of phenylephrine. The cumulative dose of phenylephrine, the number of boluses, and the median dose required to treat the first hypotensive episode, total number of hypotensive episodes, maternal side effects, neonatal appearance, pulse, grimace, activity, and respiration (APGAR) scores, and umbilical arterial cord blood pH were noted. Statistical analysis was done using Student's t-test, Mann–Whitney U-test, Chi-square test/Fisher's exact test as appropriate. A $P < 0.05$ was considered significant.

Results: The cumulative dose and number of boluses of phenylephrine required to treat post-spinal hypotension were comparable. The median dose required to treat the first episode of post-spinal hypotension was also similar ($p = 0.792$). The time to develop the first hypotensive episode was significantly earlier for group N ($p = 0.002$). The efficacy of a single fixed bolus of 50 μg phenylephrine was similar in both groups ($p = 1.000$). Neonatal median APGAR scores at 1 min after birth were significantly higher for group N ($p = 0.016$).

Conclusion: A fixed-dose bolus of 50 μg phenylephrine is safe and effective in treating post-spinal hypotension in pre-eclampsia. The efficacy of phenylephrine is comparable in pre-eclamptic and normotensive parturients.

Keywords: Drug therapy, hypotension, phenylephrine, pre-eclampsia, vasoconstrictor agents

Introduction

Spinal block is the commonest anesthetic technique for patients undergoing cesarean section (CS). Post-spinal hypotension remains a common sequela of the block and can lead to severe maternal as well as fetal side effects. These include impaired utero-placental perfusion leading to fetal hypoxia, acidosis, and neonatal depression.[1] Prevention, control, and management of post-spinal hypotension are thus an accepted clinical goal.

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Various interventions like intravenous (IV) fluid administration, reduced dose of local anesthetics with or without adjuvants, leg compression or elevation, and left uterine displacement have been tested for prevention or management of hypotension.[2] The mainstay for treatment of post-spinal hypotension however is vasopressors. Among the various vasopressors, phenylephrine, direct-acting α1 agonist, produces vasoconstriction and improves the systolic and diastolic pressures in the mother while producing lesser fetal acidosis compared to ephedrine[3] and is now the first-line agent for the management of post-spinal hypotension.[4–8] Parturients with severe pre-eclampsia are six times less likely to develop post-spinal hypotension compared to their healthy counterparts.[9] However, since there is an increased vascular reactivity in this group of patients exaggerated responses to vasopressors may be seen. Hence, a lower dose of phenylephrine is recommended for the management of post-spinal hypotension in pre-eclamptics. Despite this recommendation, we could not locate any evidence evaluating and comparing the effective doses in pre-eclamptic versus normotensive patients undergoing CS. Further, there is no comparison of the usual bolus dose of phenylephrine (50 μg) between the two groups of patients. This study was thus aimed to evaluate and compare the efficacy of a 50 μg bolus of phenylephrine for treatment of post-spinal hypotension in pre-eclamptic versus normotensive parturients scheduled for CS under a spinal block. The primary objective was to compare the total dose of phenylephrine required to treat hypotension until the baby's delivery. The secondary objectives were to compare the dose of phenylephrine required to treat the first episode of hypotension, the efficacy of a single bolus dose of phenylephrine to treat hypotension, the total number of hypotensive episodes, neonatal umbilical cord blood pH, and maternal complications.

Material and Methods

This prospective comparative study was conducted in the Department of Anesthesiology in a tertiary care teaching medical college after obtaining approval from the Institutional Ethical Committee - Human Research (vide letter no. IEC-HR/2018/33/1R dated March 19, 2018). The trial was prospectively registered with ctri.nic.in. (CTRI/2018/03/012890 on March 27, 2018). A written, informed consent was obtained from all the participants.

Previously healthy parturients with age between 18 and 40 years with singleton term pregnancy, scheduled to undergo CS under single-shot spinal anesthesia, were included. Patients with a history of diabetes, cardiovascular or cerebrovascular diseases, placenta previa, abruptio placenta, fetal abnormalities, cord prolapse or nuchal cord, fetal malformations, fetal distress, and those having any contraindication to spinal anesthesia were excluded.

Pre-eclampsia was defined as blood pressure (BP) ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 h apart after 20-week gestation with proteinuria or in absence of proteinuria accompanied by new-onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, new-onset headache, or visual symptoms. Severe pre-eclampsia was defined as BP ≥160/110 mm Hg on two or more occasions at least 4 h apart or thrombocytopenia (platelet count $<100 \times 10^9$/l), pulmonary edema, new-onset cerebral or visual disturbances, impaired liver function, or a serum creatinine concentration >1.1 mg dl^{-1} or more than twice the baseline serum creatinine concentration.[10] Patients with pre-eclampsia or severe pre-eclampsia were allocated to group P and the otherwise healthy normotensives were allocated to group N.

All patients received ranitidine 50 mg and metoclopramide 10 mg IV before wheeling into the operating room. In the operating room, electrocardiography, pulse oximetry, and non-invasive BP monitors were attached. Heart rate, systolic blood pressure (SBP), diastolic blood pressure, mean blood pressure, and peripheral oxygen saturation were measured, and an average of three readings was recorded as the respective baseline value. IV access was secured with an 18G cannula and balanced salt infusion initiated at 10 ml kg^{-1} as pre-loading and co-loading.

Under all aseptic precautions, spinal anesthesia was administered with the patient in a sitting position using a 25G Whitacre needle. Hyperbaric bupivacaine in a dose of 10 mg or 12.5 mg (0.5%) was injected for patients with height <150 cm or greater, respectively. The patients were then made supine and a wedge placed under the right hip to maintain left uterine displacement. Time taken to make the patient supine was noted. Hemodynamic parameters including heart rate, systolic, diastolic, and mean BP were recorded when the patient was put in the supine position and subsequently every minute till baby delivery, followed by every 5 min thereafter till completion of surgery. The level of the block was assessed by complete loss of sensation to pinprick using a 26G hypodermic needle in the midline at 5 min and 20 min after spinal injection.

Post-spinal hypotension was defined as mean arterial blood pressure (MAP) ≤70% of baseline value in both the groups; and also an SBP <100 mm Hg, whichever was higher, as an additional definition in the normotensive group. The

incidence of post-spinal hypotension was observed from the time interval after giving spinal anesthesia till the delivery of the baby in both groups.[9] Hypotension was treated with IV phenylephrine 50 μg fixed bolus. Further fixed boluses of 50 μg phenylephrine were administered every minute till the blood pressure recovered to SBP >100 mm Hg or MAP >70% of baseline (i.e., above the hypotensive threshold of the patient). This was considered as one hypotensive episode. A subsequent fall in systolic or mean BP (as described previously) after recovery was counted as a fresh episode of hypotension and managed similarly.

Sample for umbilical arterial blood gas analysis was obtained from a segment of umbilical cord double clamped before baby's first breath.

For comparing the efficacy of phenylephrine, cumulative dose of phenylephrine required to treat post-spinal hypotension during the entire study period (from intrathecal injection till delivery of the baby), as well as the amount required to treat the first episode of hypotension and its effectiveness for the same was recorded. Additionally, the time to development of the first hypotensive episode and the total number of hypotensive episodes were also noted. Maternal adverse effects including bradycardia (heart rate <60/min) and reactive hypertension (increase in mean blood pressure >20% from baseline) were observed as well. Bradycardia was managed using glycopyrrolate 0.2 mg IV if the heart rate was <50/min. Neonatal outcome in terms of the appearance, pulse, grimace, activity, and respiration (APGAR) scores at 1 min and 5 min after birth, and the umbilical arterial cord blood pH was also observed. Any incidence of nausea/vomiting in the period between the spinal block and baby delivery was noted and treated according to standard protocols.

Sample size and statistical analysis

At the time of designing this study, there was a lack of published data on the effective dose of phenylephrine required to treat hypotension in pre-eclamptic parturients. Hence, the study was conducted as a pilot study with 30 patients who developed post-spinal hypotension included in each group (60 total).

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20.0. Normally distributed quantitative variables were reported as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed variables were expressed as median [inter-quartile range, IQR] and compared using Mann–Whitney U-test. Qualitative parameters were compared using the Chi-square test/Fisher's exact test as appropriate. A $P < 0.05$ was taken as statistically significant.

Results

A total of 98 parturients were screened of whom five did not meet the inclusion criteria [Figure 1]. Of the 93 patients included, 51 were pre-eclamptics and 42 normotensives. Among these, 21 pre-eclamptic and 12 normotensive patients did not experience intraoperative post-spinal hypotension during the CS. Thus, the remaining 30 pre-eclamptic (group P) and 30 normotensive patients (group N) who experienced post-spinal hypotension were included to receive the intervention, and their data were analyzed [Figure 1].

In group P, nine out of 30 (30%) had manifestations of severe pre-eclampsia and were receiving magnesium sulfate for seizure prophylaxis in addition to antihypertensive therapy. Both the groups were statistically similar with regard to the baseline demographic characteristics [Table 1]. A comparison of intraoperative details [Table 2] including spinal block characteristics showed a similar time to perform the block, sensory block level 5 min later, time to delivery, and blood loss ($P > 0.05$). However, the level of sensory block was significantly lower at 20 min and the volume of IV fluids infused intraoperatively was lesser for group P as compared to group N.

The baseline mean heart rate ($P = 0.006$), systolic, diastolic, and mean BP ($P < 0.001$) were significantly higher in

Table 1: Demographic characteristics

	Group P (n=30)	Group N (n=30)	P
Age* (yr.)	25.00 [24.00-27.75]	26.00 [24.75-28.00]	0.443
Height* (cm)	156.00 [154.50-158.00]	153.50 [151.50-155.00]	0.001
Weight† (kg)	64.79±6.08	63.36±4.93	0.328
ASA‡ (I:II:III)	0:26:4	23:7:0	<0.001

*ASA=American Society of Anesthesiology. *Values are expressed as median [IQR]; †Values are expressed as mean±SD; ‡Values are expressed as ratio*

Table 2: Subarachnoid block and intraoperative characteristics

	Group P (n=30)	Group N (n=30)	P
Time to make the patient supine (s)	15 [10.0-25.0]	15.25 [10.00-16.25]	0.206
Sensory level at 5 min post-block	T6 [T6-T6]	T6 [T6-T6]	0.205
Sensory level at 20 min post-block	T5 [T4-T6]	T4 [T4-T4.5]	0.013
Completion of spinal-delivery interval (min)	8.0 [5.0-10.0]	9.0 [5.0-11.0]	0.888
Supine to delivery interval (min)	11.0 [8.25-14.05]	13.0 [9.0-16.25]	0.297
Blood loss (ml)	500.0 [475.0-800.0]	500.0 [425.0-600.0]	0.597
Volume of IV fluid (ml)	1275.0 [1000.0-1500.0]	1500.0 [1200.0-2000.0]	0.008

Values are expressed as median [IQR]

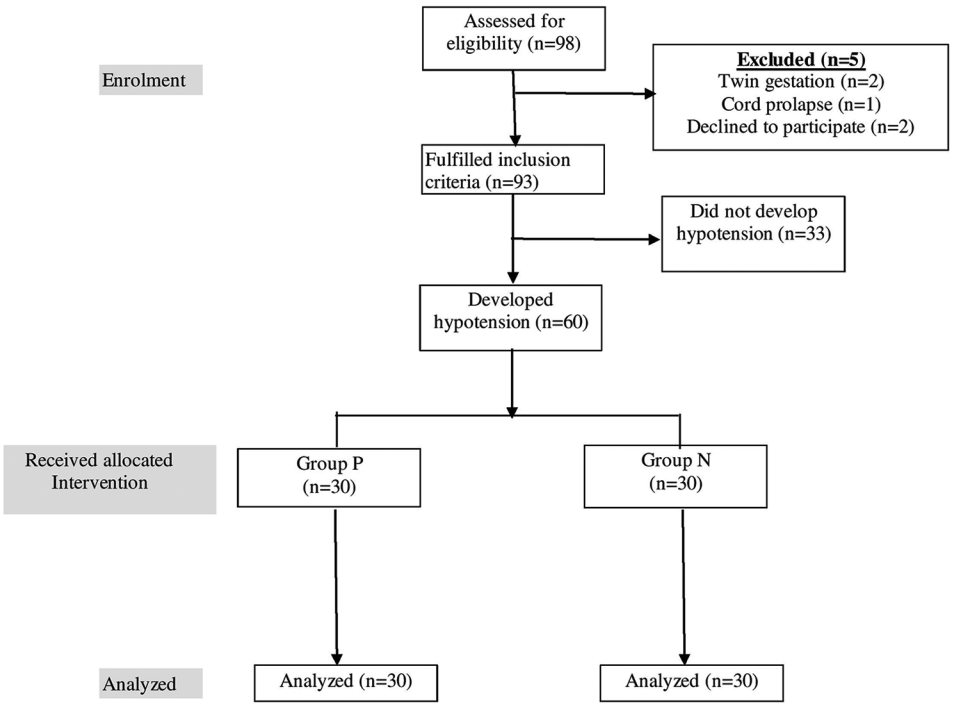

Figure 1: Flow chart of patient enrollment

group P compared to group N [Table 3]. For group P, the baseline heart rate was significantly higher, while the percentage increase in heart rate was significantly lower [maximum heart rate-baseline heart rate/baseline heart rate) ×100] as compared to group N [Table 3]. Baseline systolic, diastolic, and mean BP was higher in group P compared to group N. There was no difference in the lowest recorded mean BP and the percentage reduction in the mean BP from the baseline [Table 3].

The cumulative dose (or thus the number of boluses) of phenylephrine required to treat post-spinal hypotension during the entire study period was clinically lesser, although statistically similar, for group P as compared to group N [Table 4, Figures 2 and 3]. The amount of phenylephrine required to treat the first episode of post-spinal hypotension was similar for both groups [$p = 0.792$, Table 4]. The number of hypotensive episodes was statistically similar between both groups, though the time to develop the first hypotensive episode was significantly earlier for group N ($P = 0.002$, Table 4). A single fixed bolus of 50 μg phenylephrine was found to be effective in a statistically similar number of patients in both the groups, defined as successfully raising the BP to above the hypotensive threshold within a minute of administration [Table 4]. The Kaplan–Meier survival curves for time to hypotension of both groups are shown in Figure 4. The median time for the survival function was 8 (5.9–10.0) min and 5 (2.5–7.4) min in group P and group N, respectively ($P = 0.246$).

Neonatal median APGAR scores at 1 min after birth were significantly higher for group N as compared to group P. Rest of the neonatal parameters were statistically similar between both groups [Table 5]. Percentage of patients with bradycardia and rebound hypertension were clinically higher but statistically similar for group N as compared to group P (16.7% versus 0%; $P = 0.052$ and 3.3% versus 0%, $P = 1.000$, respectively). The incidence of nausea/vomiting was similar for both groups (3.3% each). The overall incidence of maternal side effects was statistically similar between both groups ($P = 0.091$), Table 6.

Discussion

The present study aimed to evaluate the efficacy of a fixed-dose bolus of phenylephrine (50 μg IV) for treatment of post-spinal hypotension during cesarean delivery in pre-eclamptic versus normotensive parturients. The dose requirement of phenylephrine as well its efficacy for treating the hypotension were noted to be similar between both the groups. There was no significant difference in the associated maternal side effects; however, the neonatal APGAR score for normotensives was significantly higher at 1 min after birth.

Phenylephrine has been advocated as first-line therapy for prevention and treatment of post-spinal hypotension during CS,[11] consequent to its favorable effect on maintaining maternal hemodynamics along with umbilical pH. However,

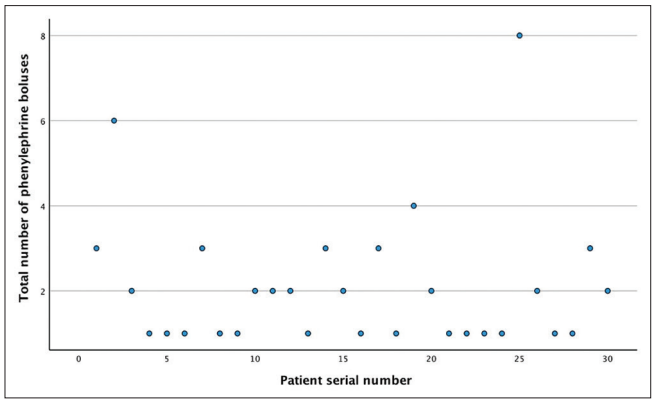

Figure 2: Scatter diagram showing the distribution of the number of phenylephrine boluses in pre-eclamptic patients

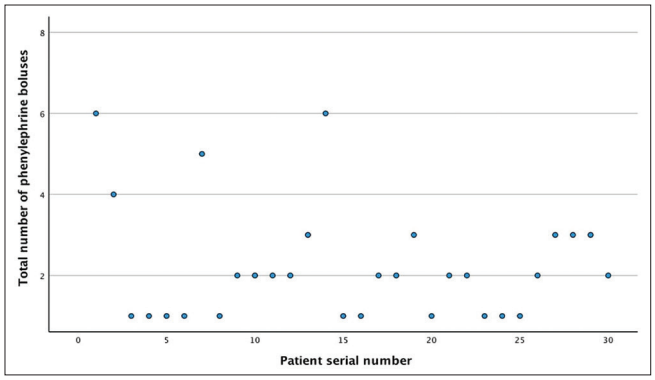

Figure 3: Scatter diagram showing the distribution of the number of phenylephrine boluses in normotensive patients

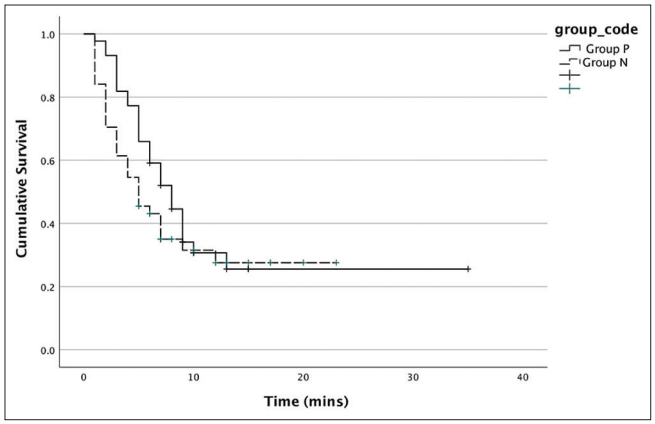

Figure 4: Kaplan–Meier survival curves for time to hypotension

most of the data for this recommendation comes from studies conducted in low-risk cesarean deliveries. Pre-eclampsia is a specific obstetric condition that poses a high-risk pregnancy. A few recent studies are evaluating the use of phenylephrine in this group of patients. In these studies, a fixed bolus dose of 50 μg phenylephrine was found to be as efficacious as ephedrine in treating post-spinal hypotension in pre-eclamptic parturients.[12–14] However, we could not locate any data comparing the efficacy of phenylephrine for the treatment of post-spinal hypotension between pre-eclamptics and normotensives.

The effective dose 95 (ED95) of phenylephrine in parturients with normal BP is 122 μg[15] and the recommended bolus dose is 50–100 μg.[1,16] When observational cohorts of

Table 3: Intraoperative hemodynamic characteristics

	Group P (*n*=30)	Group N (*n*=30)	*P*
Baseline heart rate*	99.63±14.90	88.61±14.76	0.006
% increase in heart rate from baseline†	9.62 [−15.51-23.39]	18.34 [−4.71-40.13]	0.014
% decrease in heart rate from baseline*	23.17±12.35	20.98±15.63	0.552
Baseline SBP*	140.90±10.86	123.07±11.14	<0.001
Baseline diastolic blood pressure*	88.17±9.57	77.80±8.01	<0.001
Baseline mean blood pressure*	105.73±9.77	94.54±7.71	<0.001
Lowest mean blood pressure*	69.33±8.28	65.03±8.55	0.053
% decrease in mean BP from baseline*	34.19±7.51	30.93±9.68	0.150

**Values are expressed as mean±SD; †Values are expressed as median [IQR]*

Table 4: Hypotension and phenylephrine-related parameters

	Group P (*n*=30)	Group N (*n*=30)	*P*
Cumulative phenylephrine dose* (μg)	75.00 [50.00-150.00]	100.00 [50.00-150.00]	0.411
Dose of phenylephrine required to treat first hypotensive episode* (μg)	50.0 [50.0-100.0]	50.00 [50.00-100.00]	0.792
Number of hypotensive episodes*	1.00 [1.00-2.00]	1.00 [1.00-2.00]	0.993
Time to develop first hypotensive episode* (s)	5.50 [3.00-8.00]	3.00 [1.75-5.00]	0.002
Phenylephrine boluses required till baby delivery*	2 [1.00-2.75]	2 [2.00-5.00]	0.512
No. (%) of cases where single bolus was effective in treating first hypotensive episode†	20 (66.67)	19 (63.33)	1.000

**Values are expressed as median [IQR]; †Values are expressed as number (percentage)*

Table 5: Neonatal characteristics

	Group P (*n*=30)	Group N (*n*=30)	*P*
APGAR @ 1 min*	9.0 [9.0-9.0]	9.5 [9.0-10.0]	0.016
APGAR @ 5 min*	10.0 [10.0-10.0]	10.0 [10.0-10.0]	0.643
pH†	7.27±0.09	7.31±0.07	0.055
PO_2* (mm Hg)	30.6 [26.9-34.8]	23.9 [19.9-34.5]	0.051
PCO_2* (mm Hg)	38.25 [32.37-42.65]	38.5 [33.6-41.9]	0.831
Birth weight* (kg)	2.50 [2.30-2.70]	2.50 [2.20-2.80]	0.790
Incidence of neonatal acidosis‡ (pH <7.2)	04 (0.13)	02 (0.06)	0.740

**Values are expressed as median [IQR]; †Values are expressed as mean±SD; ‡Values are expressed as number (percentage)*

Table 6: Intraoperative complications

Complications	Group P (n=30)	Group N (n=30)	P
Bradycardia	0 (0)	4 (0.13)	0.091
Reactive hypertension	0 (0)	1 (0.03)	
Nausea	1 (0.03)	1 (0.03)	

Values are expressed as number (percentage)

pre-eclamptics and normotensives undergoing CS were evaluated, it was witnessed that the incidence of post-spinal hypotension was lesser and the need for phenylephrine was lower for pre-eclamptics, although the dosage for pre-eclamptics was not standardized.[17] Based on this earlier observation of lesser incidence of hypotension and the need for phenylephrine for pre-eclamptics, we chose a dose of 50 μg rather than 100 μg as a bolus in both groups.

The trend we noted of pre-eclamptics having a lesser incidence of post-spinal hypotension, and developing it later points to a sort of resistance towards post-spinal hypotension. In our study, 42 normotensive parturients and 51 pre-eclamptics were enrolled to obtain the requisite number of 30 parturients who developed post-spinal hypotension in each group. The estimated incidence of post-spinal hypotension from our study is 71.43% in normotensives and 58.82% in pre-eclamptics. This supports the previous findings that the incidence of post-spinal hypotension is lower in pre-eclamptics.[9,18] We found that the first episode of hypotension occurred significantly later in pre-eclamptic compared to normotensive parturients (5.5 versus 3 min, respectively), although the total number of hypotensive episodes was similar between both groups. This corroborates well to the time to first bolus administration of vasopressor determined in the study by Wang *et al.*[14]

The total dose of phenylephrine required to treat hypotension was statistically similar in the two groups, even though it was clinically lesser for the pre-eclamptics versus normotensives (75 μg versus 100 μg, respectively). This points towards a trend of lower dose requirements in pre-eclamptics than normotensive parturients, which would be supported by the trend of resistance to post-spinal hypotension observed by us.[9,17] Another ancillary observation that could support greater sensitivity to phenylephrine among the pre-eclamptics is the clinically higher incidence of a successful response to the first dose of phenylephrine (66.67% patients in the pre-eclampsia group compared to 63.33% in the normotensive group). Also, this was only a pilot study and not powered to detect differences in the cumulative dose requirement. Thus, it appears that there may be a trend towards a greater sensitivity to phenylephrine among pre-eclamptics. The current pilot study thus serves the purpose of generating a hypothesis for further testing in adequately powered trials.

The neonatal parameters were comparable among the groups except for the APGAR score at 1 min which was lesser in pre-eclamptic parturients although none of the values was ≤7.0. As seen from this study, the babies born to pre-eclamptic parturients have neonatal parameters comparable to those born to normotensive parturients. However, our study was not powered to calculate the statistical significance of neonatal outcomes.

Various definitions of hypotension in pre-eclampsia have been used in different studies. However, we adopted the criteria used by Aya *et al.*[9] taking into account both, a MAP ≤70% and additionally, SBP <100 mm Hg in the normotensive group. The reason for the same was because the baseline BP in pre-eclamptic parturients is in a higher range as compared to normotensive counterparts. Keeping the cutoff for management of hypotension to an absolute value of SBP <100 mm Hg in those having 140–160 mm Hg systolic pressure would mean a fall of approximately 28–37.5% in the SBP, which is quite higher than the 20% fall as incorporated in many of the definitions of spinal-induced hypotension.[13,14] Withholding the administration of vasopressor till this value could have had a further detrimental effect on the already lower value of APGAR score, pH, PO2 observed in pre-eclamptic parturients. Considering these criteria to guide vasopressor therapy did not increase the incidence of reactive hypertension in our study. The incidence of nausea and vomiting, which are mainly due to significant hypotension, was also negligible probably due to the defined cutoff for managing hypotension. Many other definitions of hypotension in pre-eclamptic parturients are also being practiced[12] resulting in varying results on the efficacy of the drug. The recent consensus guidelines talk about maintaining SBP ≥90% of the baseline and not on an absolute cutoff of 100 mm Hg.[11]

The study has a few limitations. First, since it was a pilot study, it was not powered to detect a difference between the neonatal outcomes. Second, both mild and severe pre-eclamptics were included and some of them were also receiving magnesium sulfate. The effect of magnesium sulfate on the hemodynamic variables was not studied separately. Third, a fixed bolus dose of phenylephrine was used, rather than the up and down method. A better design would have been a dose-response study for the determination of ED50 of phenylephrine for pre-eclamptic parturients.

Conclusion

Based on the findings of the study, we conclude that a fixed-dose bolus of 50 μg phenylephrine is safe and effective in treating post-spinal hypotension in pre-eclampsia.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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