Original Article

Effect of intravenous phenylephrine infusion on dose requirement of intrathecal plain levobupivacaine for cesarean section: A placebo-controlled preliminary study

ABSTRACT

Background: Phenylephrine infusion has been shown to decrease rostral spread of plain and hyperbaric local anesthetic (LA) when compared to ephedrine infusion. However, it does not result in higher dose requirement of hyperbaric LA for cesarean section. There is no trial evaluating the effect of phenylephrine infusion on ED50 of a plain intrathecal LA.

Methods: Pregnant patients with term uncomplicated singleton pregnancy undergoing elective cesarean section were given combined spinal-epidural anesthesia. They received intrathecal plain levobupivacaine 0.5% in a dose decided by up-and-down sequential allocation method along with 25 μg fentanyl. Intravenous infusion of phenylephrine (100 μg/ml) or normal saline was initiated immediately after intrathecal injection. Systolic arterial pressure ≤0.8 times baseline was treated using rescue boluses of phenylephrine 50 μg.

Results: Demographic, other patient and surgical characteristics were similar in the two groups. ED50 of intrathecal plain levobupivacaine was significantly greater in phenylephrine group (5.5 mg [95% confidence interval (CI): 5.1–5.9 mg]) compared to saline group (4.2 mg [95% CI: 3.4–5.1 mg]) ($P = 0.01$). Maximum sensory level, time to achieve adequate block, Apgar scores, and umbilical artery pH were similar in both groups. Total phenylephrine dose and patients having significant bradycardia were lesser in the saline group.

Conclusions: Intrathecal dose requirement of plain levobupivacaine is greater using phenylephrine infusion as compared to saline infusion with rescue phenylephrine boluses. When using phenylephrine as a variable dose regimen titrated to maintain blood pressure within 20% of baseline, the ED50 of plain levobupivacaine is 5.5 mg (95% CI: 5.1–5.9 mg).

Key words: Cesarean section; ED50; phenylephrine infusion; plain levobupivacaine; spinal anesthesia

Introduction

Postspinal hypotension is common during cesarean section and is a concern due to its adverse maternal and fetal consequences.[1] From among the various methods used to prevent or treat it, vasopressors remain a mainstay therapy.

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It has been shown previously that the choice of vasopressor therapy for managing postspinal hypotension during cesarean section affects the rostral spread of intrathecal local anesthetic (LA).[2-4] Comparison of phenylephrine versus ephedrine infusion showed decreased rostral spread of plain[2,4] as well as hyperbaric LA with phenylephrine.[3,4] Consequent to the decreased rostral spread of intrathecal LA with phenylephrine infusion, the ED50 of hyperbaric bupivacaine for cesarean section was investigated with the results showing lack of anticipated increase in dose requirement.[5] There is however no trial evaluating the effect on ED50 of a plain intrathecal LA.

Furthermore, all earlier comparisons for effect of vasopressor on the spread of intrathecal LA evaluated phenylephrine versus ephedrine.[2-5] In current obstetric anesthetic practice, phenylephrine is recommended over ephedrine and is thus often used as first-line vasopressor for prevention and treatment of maternal hypotension due to the maintenance of better fetal acid-base status.[1]

Against this background, the present placebo-controlled trial aimed to evaluate the effect of prophylactic phenylephrine infusion used to prevent postspinal hypotension, on the dose requirement of intrathecal plain levobupivacaine for elective cesarean section. The intrathecal dose requirement was assessed as the ED50, evaluated using up-and-down sequential allocation method.[6]

Methods

This prospective, randomized, double-blinded trial was conducted after obtaining approval from the Institutional Ethical Committee (IEC) and written informed consent from the patients. The trial was registered with the Clinical Trial Registry of India (CTRI/2015/10/006242).

Originally, this study was planned and thus registered with CTRI, using plain bupivacaine and not levobupivacaine. However, by the time we actually started recruitment, preservative-free plain bupivacaine (0.5%) was not being manufactured any longer. The manufacturer had instead launched preservative-free plain levobupivacaine (0.5%). Since levobupivacaine is an enantiomer of bupivacaine with similar properties, but only with a higher safety profile, we carried out the trial using original methodology cleared by the IEC for plain bupivacaine.

The trial was conducted in pregnant patients scheduled for elective cesarean section with an uncomplicated singleton pregnancy of 37 weeks or greater gestation. Those with extremes of height or weight (body mass index [BMI] <20 kg/m^2 or >35 kg/m^2, height <145 cm or >180 cm), pregnancy-induced hypertension, history of diabetes mellitus, cardiovascular or cerebrovascular diseases, fetal abnormalities, any contraindication to combined spinal-epidural block, or who refused consent were excluded from the study.

Individuals were randomized using computer-generated random number table to either of two groups: the phenylephrine group that received a prophylactic intravenous infusion of the vasopressor (100 μg/ml) or the saline group that received a normal saline infusion as placebo (0.9%). Either of these test infusion, allocated as per randomization, was initiated at the time of completion of the intrathecal injection.

For all included patients, baseline values of systolic arterial pressure and heart rate were recorded in the preoperative room in sitting position, as mean of two readings taken 5 min apart with $<10\%$ variation.[5] After shifting to the operating room, monitoring including lead II electrocardiography, oscillometric noninvasive blood pressure measurements, and pulse oximetry were instituted.

Intravenous access was established with 18-gauge cannula, and all patients were infused 10 ml/kg of Ringer's lactate as coloading during the performance of the combined spinal-epidural block. Patients of both groups received the combined spinal epidural using needle-through-needle technique (Portex; Smiths Medical). With patient in sitting position, L_3–L_4 or L_4–L_5 interspace was identified, skin infiltrated with 2% lidocaine in the midline, and the epidural space identified through 18-gauge Tuohy needle by loss of resistance to air technique, limiting the volume of air to <2 ml. A 27-gauge Whitacre spinal needle was passed through the Tuohy needle to attain free flow of cerebrospinal fluid (CSF). The intrathecal solution was injected over 10–15 s after confirming free flow of CSF through the spinal needle. Following the intrathecal injection, catheter was threaded through Tuohy needle into the epidural space and fixed 4 cm inside space after confirming the absence of CSF or blood through it. No injections through epidural catheter were made at this time.

Following this, the patient was turned supine with a 15° tilt to left side and oxygen through facemask administered at 4 L/min.

The dose of intrathecal levobupivacaine for each patient was decided by the up-and-down sequential allocation method

wherein the first patient in both groups received 8 mg of plain levobupivacaine (0.5%), along with 25 μg fentanyl. After an adequate block, the next patient in that group received a dose reduced by 1 mg of levobupivacaine, and in case of an inadequate block, the dose was increased by 1 mg for the next patient in that group. An adequate block was defined as one that resulted in a sensory block to T4 level along with motor block of modified Bromage score[7] = 1 or 2, achieved within 15 min of intrathecal injection. The sensory level of block was assessed by complete loss of sensation to pinprick in the midline. For motor blockade, the modified Bromage score included 1 = complete block, unable to move feet or knees; 2 = almost complete block, able to move feet only; 3 = partial block, just able to move knees; 4 = detectable weakness of hip flexion while supine, full flexion of knees; 5 = no detectable weakness of hip flexion while supine; and 6 = able to perform partial knee bend.

Both the sensory and motor block characteristics were noted every 3 min until two identical readings were obtained, or 15 min after intrathecal injection elapsed, whichever was later. This marked the end of study period, and beyond this time, the continuation of test infusions was left at the discretion of attending anesthesiologist. The blood pressure was also recorded every 2 min during the study period, followed by intervals of 5 min as for routine anesthetic management.

For blinding purposes, an anesthesiologist who was otherwise not involved in the trial prepared the test infusion as per group allocation. Furthermore, the anesthesiologist who noted all outcome measures and observations as well as managed the rates of test infusion was separate from the one who performed the block; being unaware of group allocation as well as details of intrathecal dose. The rate of delivery of the test infusion, i.e., phenylephrine or normal saline was titrated to the patients' blood pressure as per following protocol used in an earlier relevant study.[2] The intravenous infusion was started at 40 ml/h in both groups using a syringe infusion pump (i.e., 66.7 μg/min of drug in patients receiving phenylephrine). The rate of infusion was changed by factors of two, i.e., doubled or halved, as required to maintain the systolic arterial pressure at patient's baseline value recorded in the preoperative period. If the systolic arterial pressure increased above 1.2 times the baseline, the infusion was stopped and recommenced at half the rate when the systolic arterial pressure had decreased below 1.2 times baseline. The maximum rate of delivery of the test infusion was 40 ml/h, and the minimum was 2.5 ml/h (if less was required, the infusion was discontinued and recommenced as necessary). Fall in systolic arterial pressure to 0.8 times or lower of baseline at any time despite test infusion on flow was treated using a rescue bolus of intravenous phenylephrine 50 μg. If there was no improvement in systolic blood pressure, repeat boluses were given. Bradycardia was defined as a heart rate of <60/min with hypotension or <50/min and treated with 200 μg glycopyrrolate given intravenously.

In case the intrathecal block was inadequate or if intraoperative pain occurred (visual analog scale >3), epidural injections of bupivacaine (0.5%) were used in increments of 3–5 ml.

Ancillary observations included the time to attain adequate block, times between intrathecal injection and delivery, uterine incision and delivery, and between intrathecal injection and making patient supine as well as the duration of surgery. Furthermore, the number of patients requiring boluses of phenylephrine or glycopyrrolate, the age, height, weight, BMI, period of gestation, Apgar scores at 1 and 5 min, umbilical arterial pH, and neonatal birth weight were noted.

Statistical tests

The up-and-down sequences were analyzed using the formula of Dixon and Massey which enabled ED50 with 95% confidence interval (CI) to be calculated.[6] Normally distributed quantitative parameters were compared using *t*-test. The maximum sensory block level and Apgar scores were nonnormal in distribution and were thus compared using Mann–Whitney test. $P < 0.05$ was considered statistically significant.

Sample size

Using the up-and-down methodology, 6 pairs of reversal constitute an adequate sample size.[8]

The up-and-down methodology is an excellent procedure for determining the ED50, with another advantage being reduction in required sample size. The disadvantage is that it is not good for extremes such as an ED90 or ED95. We have seven reversal pairs in the test group.

Table 1: Demographic data and baseline characteristics

Parameter	Saline group ($n=18$)	Phenylephrine group ($n=18$)	*P*
Age (years)	26.2±3.6	26.1±3.4	0.88
Height (cm)	156±5	155±5	0.34
Weight (kg)	62.3±9.4	61.2±8.9	0.73
Period of gestation	38.3±1.2	38.6±1.2	0.59
BMI (kg/m^2)	25.6±3.8	25.5±2.8	0.92
Basal systolic blood pressure (mmHg)	122±8	120±7	0.43
Basal heart rate (/min)	90±14	91±15	0.89

Data are mean±SD. BMI: Body mass index; SD: Standard deviation

The ED50 of levobupivacaine for successful sensory and motor block both during cesarean section has not been determined previously. The required sample size taking into account ED50 of hyperbaric bupivacaine with the use of phenylephrine from an earlier published evidence,[5] to detect a difference of 2 mg (significant difference 2 mg) as significant, yields 17 patients in each group at a power of 80% and an alpha error of 5%. We used this calculation as a backup measure and decided to enroll a minimum of 18 patients. The present results can serve as preliminary study to guide larger adequately sized clinical trial.

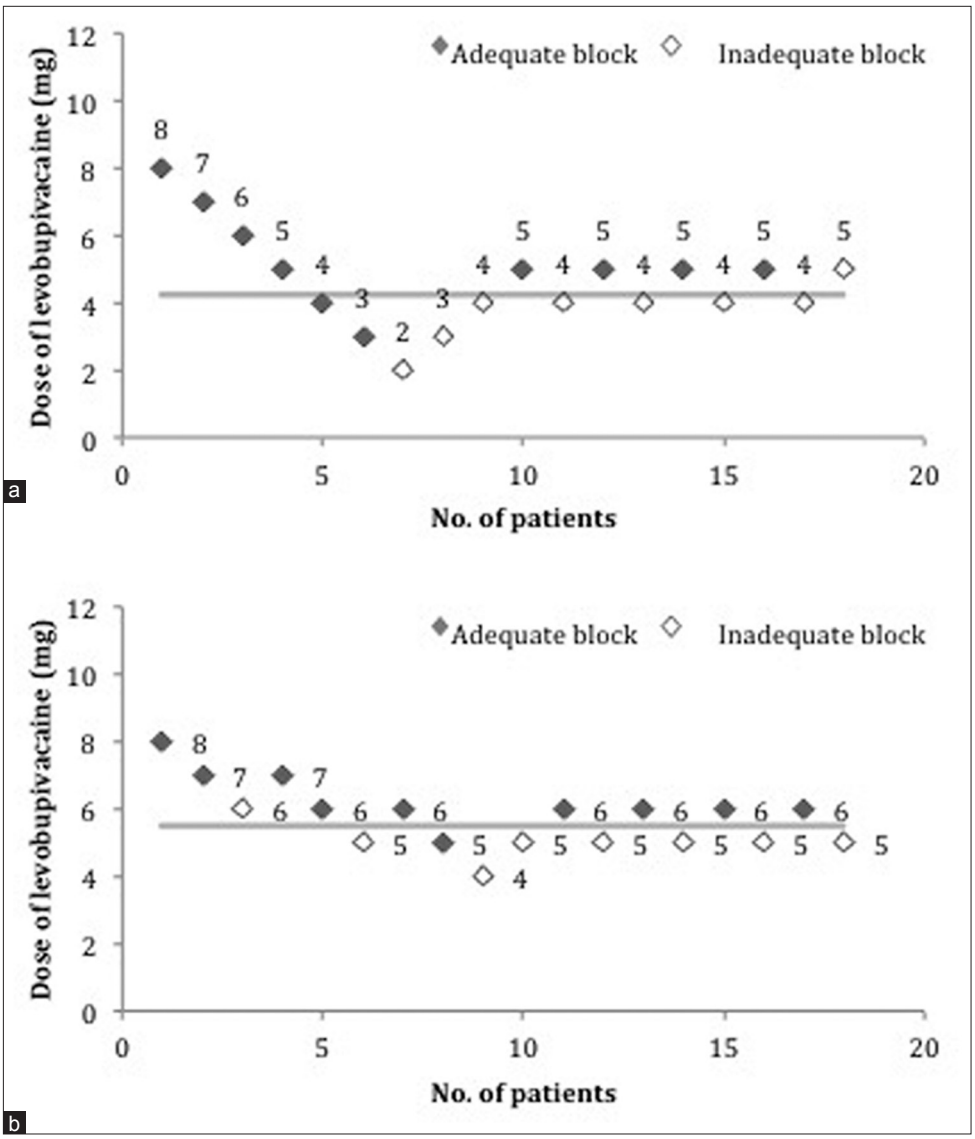

Figure 1: Sequences of doses of levobupivacaine for (a) placebo saline group, with ED50 and (b) phenylephrine group, with ED50

Table 2: Block characteristics in patients with adequate block

	Saline group (n=10)	Phenylephrine group (n=10)	P
Maximum sensory level	T4 (3-4)	T4 (3-4)	0.85
Time to adequate block (min)	8.6±2.7	9.5±2.9	0.50
Time from intrathecal injection to supine position (s)	122±46	137±31	0.42
Time from intrathecal injection to delivery (min)	18.7±7.0	15.8±4.3	0.28
Time from uterine incision to delivery (min)	1.8±1.4	1.7±1.1	0.79
Duration of surgery (min)	64.4±20.4	56.2±20.5	0.38

Data are mean±SD or median (IQR). SD: Standard deviation; IQR: Interquartile range

Results

The demographic parameters and baseline characteristics were statistically similar between the saline and phenylephrine groups [$P > 0.05$, Table 1].

The sequences of doses for adequate and inadequate blocks for both groups are shown in Figure 1. The ED50 of intrathecal plain levobupivacaine was significantly greater in the phenylephrine group (5.5 mg [95% CI: 5.1–5.9 mg]) as compared to the saline group (4.2 mg [95% CI: 3.4–5.1 mg]) ($P = 0.01$).

The block characteristics were compared between both groups for patients with an adequate block. These included the maximum sensory level, time to achieve adequate block, time from intrathecal injection to putting patient in the supine position as well as delivery of the baby, time from uterine incision to delivery and the duration of surgery, all of which were statistically similar between both groups [Table 2; $P > 0.05$].

The dose of phenylephrine was significantly greater in the phenylephrine group as compared to saline group (805 [720–1154] vs. 75 [37–125]; $P = 0.00$). The number of patients requiring one or more boluses of phenylephrine was significantly greater in the saline group as compared to phenylephrine group (12/18 vs. 1/18; $P = 0.002$). The number of patients requiring glycopyrrolate administration for treatment for bradycardia was lesser in saline than phenylephrine group (4/18 [22%] versus 7/18 [39%], respectively, [$P = 0.71$]). The parameters of neonatal outcomes were statistically similar between both groups [Table 3; $P > 0.05$].

Discussion

This trial aimed to evaluate the effect of prophylactic phenylephrine infusion when used to prevent postspinal hypotension, on the dose requirement of intrathecal plain levobupivacaine for elective cesarean section. We observed that ED50 of intrathecal plain levobupivacaine was significantly greater with the use of phenylephrine as compared to placebo saline infusion (5.5 mg vs. 4.2 mg) ($P = 0.01$).

Table 3: Neonatal outcome in patients with adequate block

Parameter	Saline group ($n=10$)	Phenylephrine group ($n=10$)	*P*
Apgar score (1 min)	9 (9-9)	9 (8-9)	0.53
Apgar score (5 min)	9 (9-9)	9 (9-9)	1.00
Baby weight (kg)	3.0±0.5	2.6±0.5	0.13
Umbilical arterial pH	7.24±0.09	7.32±0.11	0.13

Data are mean±SD or median (IQR). SD: Standard deviation; IQR: Interquartile range

The greater levobupivacaine dose requirement with phenylephrine infusion is most likely an effect of the epidural venous constriction caused by phenylephrine infusion. This would be the same mechanism used to explain decreased rostral spread of intrathecal drug when using phenylephrine. Earlier literature has compared intrathecal drug spread with the use of phenylephrine and ephedrine infusions to prevent hypotension during cesarean section. Decrease in rostral spread of intrathecal plain levobupivacaine was noted earlier with phenylephrine infusion as compared to an ephedrine infusion.[2,4] The authors explained it by a greater constriction of the epidural venous plexus engorged due to pregnancy by phenylephrine as compared to ephedrine, thereby increasing compliance of epidural space, lowering intrathecal pressure, and reducing the spread of intrathecal injection. Other studies have noted a similar result of decreased rostral spread of intrathecal drug with hyperbaric agent as well.[3,4]

One earlier study showed a contrasting result with lack of any difference in the spread of intrathecal hyperbaric bupivacaine while comparing the effect of phenylephrine or ephedrine infusion.[9] The authors noted the use of hyperbaric rather than plain LA as the most likely reason. The spread of hyperbaric bupivacaine depends more on gravity, while for plain LA, a greater influence is exerted by bulk flow of CSF from lumbosacral to cranial region.[9] Phenylephrine reduces the bulk flow to larger extent than ephedrine thus affecting the spread of plain intrathecal drug.[2]

The effect of decreased rostral spread of intrathecal LA on its dose requirement has also been evaluated for hyperbaric bupivacaine.[5] The estimated ED50 of hyperbaric bupivacaine was similar in patients receiving phenylephrine or ephedrine infusion (7.8 mg vs. 7.6 mg), respectively. The authors suggested several reasons for the lack of dose-enhancing effect of phenylephrine. The most important one is the change in maternal position from sitting to left lateral and then to right lateral after intrathecal injection that would have resulted in gross CSF dynamic changes overriding the possibly subtle changes resulting from choice of vasopressor.[5] Our results are in contrast to this earlier study. The possible reasons could be use of a plain rather than hyperbaric intrathecal drug and patients being turned to the supine position with only a left lateral tilt as opposed to the full left and right lateral positioning.

Our results show a greater ED50 with phenylephrine infusion, but in comparison to a saline infusion. This is the first study in which phenylephrine infusion has been compared with a placebo saline one, rather than ephedrine.

Since phenylephrine boluses were used for treating systolic blood pressure decrease to <80% of baseline values in both groups, the results could also be interpreted as a comparison of preventive infusion versus therapeutic bolus regimens of phenylephrine.

The block characteristics were expectedly similar in both groups for patients with an adequate block. The median value of the maximum sensory block level in both groups was T4, approximating the cutoff defined by us for an adequate block. The time from intrathecal injection to turning patients supine from sitting position upon completion of block was similar between both groups. This suggests that the difference in dose requirement was not due to any variation in performance of the combined spinal-epidural block, a factor likely to affect block levels due to interplay between the sitting position and intrathecal drug spread.

Although the amount of phenylephrine used in the two groups was different, there was no difference in neonatal outcomes with statistically similar Apgar scores and umbilical arterial pH. However, all of these variables were compared only for patients with adequate block and hence for a very small sample size. Our study was not powered to detect the differences in these variables.

Since the clinical effects of phenylephrine are dose dependent, the results of this trial cannot be extrapolated to other regimens of the drug administration. Fixed-dose infusions as well as therapeutic boluses in various doses may yield differing ED50. We used a prophylactic infusion of phenylephrine in variable titrated dose regimen. There is evidence proving the effectiveness of prophylactic phenylephrine infusion in lowering the incidence of postspinal hypotension.[10-13] Various authors have used different infusion doses, ranging from 25 μg/min to 100 μg/min for phenylephrine and found them equally effective.[12-14] The initial rate in our study was approximately 67 μg/min.

The intrathecal dose requirement will also be affected by the definition used to describe an adequate block when using a sequential allocation method for ED50 determination.

Conclusions

Based on the current observations, it can be concluded that the intrathecal dose requirement of plain levobupivacaine is greater with the use of phenylephrine infusion as compared to a placebo saline infusion, allowing boluses of phenylephrine to treat fall in blood pressure to <80% of baseline values. When using phenylephrine as a variable dose regimen titrated to maintain blood pressure within 20% of baseline, the ED50 of plain levobupivacaine is 5.5 mg (95% CI: 5.1–5.9 mg).

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Conflicts of interest
There are no conflicts of interest.

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