



Original Research Article

Comparison of intravenous bolus doses of phenylephrine vs ephedrine along with crystalloid co-loading in the prevention of hypotension during spinal anaesthesia for caesarean section

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ABSTRACT

Background: Caesarean section was the first obstetrical operation that saves the life of the baby when normal delivery fails. Spinal anaesthesia is the most appropriate method for caesarean section. But hypotension is the most common side effect of it in patient with pregnant uterus.

Aims: To compare the vasopressor effects of ephedrine and phenylephrine in ameliorating hypotension in elective caesarean delivery receiving crystalloid coload, during intrathecal bupivacaine injection.

Materials and Methods: Study participants were randomly divided into two groups of 50 patients each. After subarachnoid block, all the parturients were given rapid administration of ringer lactate solution 20ml/kg, during the initial 5 minutes of surgery the parameters such as oxygen saturation, blood pressure and pulse rate recorded for every one minute followed by every five minutes until the completion of the surgery. The incidence of hypotension, bradycardia, nausea/vomiting, block height and requirements of vasopressor (ephedrine and phenylephrine) were recorded. Apgar score, and blood sample from umbilical cord was taken and sent for blood gas analyses to determine the neonatal outcome.

Results: Vasopressor consumption was more in phenylephrine group ($92 \pm 112 \mu\text{g}$) compared to ephedrine group ($4.8 \pm 5.5 \text{ mg}$) which was statistically significant $p=0.0001$. The neonatal outcome was statistically significant regarding umbilical cord pH (Group E- 7.2 ± 0.06 and Group P- 7.37 ± 0.04 with $p=0.002$) but clinically no true fetal acidosis in either groups and no significant changes regarding Apgar score in the two groups.

Conclusion: Thus we conclude that that ephedrine 6 mg and phenylephrine 100 μg does not differ in their efficacy to manage hypotension during spinal anaesthesia for caesarean delivery. However, maternal bradycardia was more in the phenylephrine group with equal incidence of fetal acidosis in the study groups.

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1. Introduction

Caesarean section is the earliest obstetrical operation and till today remains the only method by which babies are delivered when the normal delivery fails. It is commonly accepted that serious trauma to the baby can be eliminated

by avoiding potentially difficult mid forceps or vaginal breech deliveries by performing a caesarean section. The proportion of women undergoing caesarean section has been increasing steadily such that in Brazil, one in every two women underwent caesarean section and in the U.K, the overall incidence is 32%.¹ German surgeon Karl Bier on 16th August, 1898 first introduced Spinal

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(subarchanoid) anesthesia into clinical practice and since then, the technique has become increasingly popular.² Spinal anesthesia is the most appropriate method for caesarean section. The technique has a very rapid onset and provides a dense neural block. The reason for hypotension following spinal block is due to the vasodilatation that occurs in both arteries and veins due to the sympathetic block. As a result there will be decrease preload to heart and compensatory decrease in cardiac output. In a pregnant patients, compression of the inferior vena cava by the gravid uterus further impedes venous return; if untreated, this process may lead to maternal hypotension and uterine hypo perfusion.³

Many interventions such as leg elevation, pelvic tilt, wrapping and use of vasopressor or fluid administration have been tried to bring down the incidence of hypotension.⁴⁻⁷ Prehydration with crystalloids did not have much efficacy in preventing hypotension since it undergoes rapid distribution.⁸ Instead the use of crystalloid at the time of giving anesthesia which is called as crystalloid co loading can be more appropriate to maximize the prevention of hypotension.^{9,10} Among the vasopressors, ephedrine has been proven safe and more effective for controlling hypotension in humans.¹¹ But at higher dose it can cause significant tachycardia in mothers and fetal acidosis.¹² Hence other studies were conducted to support the use of phenylephrine with alpha agonist which showed better control of hypotension and minor change in acid base balance. Hence, the present study was designed to compare the vasopressor effects of ephedrine and phenylephrine in ameliorating hypotension in elective caesarean delivery receiving crystalloid coload, during intrathecal bupivacaine injection.

2. Materials and Methods

A prospective, randomized controlled, double blinded study with the approval by the Institutional Ethical Committee (IEC). Hundred parturients of ASA(American Society of Anesthesiologist) – I and II, weighing 50-80kgs, of height 140-170cms, having a singleton normal pregnancy more than 36 weeks of gestation, with indications for caesarean section under spinal anesthesia were taken for this study. Parturients with hypertension, diabetes mellitus, and impairment of cardiovascular or cerebrovascular function, and contraindications to spinal anaesthesia were excluded from the study. After obtaining written informed consents, the participants were divided randomly into two groups (n=50 in each) using computer generated randomization method. All were coloaded with rapid administration of Ringer's Lactate solution at the dose of 20 ml/kg once cerebrospinal fluid was confirmed.

The groups were divided as follows:-

Group E (n = 50): Parturient in Group E to receive 6 mg of intravenous bolus Ephedrine.

Group P (n = 50): Parturient in Group P to receive 100µg of intravenous bolus Phenylephrine.

On the previous day of operation, the participants were examined for pre-anesthetic fitness. Patients with co-morbidities such as hypertension, diabetes mellitus, bronchial asthma, impaired liver or renal function, coagulopathy, cardio-vascular disease were excluded from the study. Pre-anesthetic medication which included ranitidine 150 mg was administered on the night before the day of surgery. As in all other surgeries, intravenous line was set with 18G cannula in the non-dominant hand. In order to maintain patency of cannula, intravenous fluid with isotonic saline was started. For study participants, pre-anesthetic medication of metoclopramide 10 mg and ranitidine 50 mg was given through intravenous route 20 mins prior to the surgery. Before being transferred to operation theatre, baseline parameters were recorded and monitored 10 – 20 min after arrival from the ward for heart rate, systolic and diastolic blood pressure in sitting posture and oxygen saturation in pre anesthetic room.

After reaching the operation theatre, the parturients were observed with electrocardiogram (ECG), non-invasive arterial blood pressure (NIBP) and oxygen saturation (SpO₂) by pulse oximetry with the monitor 'Clarity Smart' till the end of the procedure. Base line, parameters such as oxygen saturation, heart rate, systolic and diastolic blood pressure was recorded. The L₃-L₄interspace was used for spinal anesthesia keeping the patient in left lateral using the midline approach. Sterile precaution was maintained throughout the procedure. The Quinke's needle 25G was used and dural puncture was established by the identification of cerebrospinal fluid. Once the plane of injection is established, Bupivacaine at the dose of 2 ml (10 mg) of 0.5% solution was injected at the rate of 0.2 ml/sec. Coload with rapid administration of 20 ml/kg Ringer lactate solution started simultaneously after identification of the cerebrospinal fluid with intrathecal injection. Immediately after the administration of the anesthetic agent, the parturients shifted to supine position with the operation table in horizontal plane to make the level of block upto T₆-T₄. During the initial 5 minutes of surgery the parameters such as oxygen saturation, blood pressure and pulse rate recorded for every one minute followed by every five minutes until the completion of the surgery.

The study population were randomized using computer generated randomization into two groups, group E (Ephedrine) and group P (Phenylephrine) to receive either ephedrine 6 mg intravenous bolus or phenylephrine 100 µg intravenous bolus when there is an episode of hypotension (fall in systolic blood pressure more than 20% from the baseline) in two consecutive readings. No vasopressors were given to normotensive patients. Total dose of vasopressor used in a hypotensive patients were recorded. When the patient developed bradycardia with heart rate less than

50, injection Glycopyrolate 0.2 mg i.v was administered. On delivery of the baby, after clamping the umbilical cord, the umbilical cord blood was taken in a heparinized syringe and sent for analysis for pH and Apgar score was recorded at 0,1&5 minutes for fetal well-being. Once baby is delivered, injection oxytocin was infused in normal saline along with injection methylethergometrine 0.2mg in divided dose through intramuscular and intravenous route. Baseline hemodynamic parameters, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, fall of > 20% systolic blood pressure from baseline value, bradycardia, intraoperative nausea and vomiting, block height, ephedrine and phenylephrine requirements intra operatively, Apgar score of the baby and the umbilical cord blood pH were all monitored and recorded. Chi-square test was used for comparing the categorical variable and Student T-test for continuous variables and $p \leq 0.05$ was considered significant.

3. Results

The study was conducted in 100 (hundred) parturients who underwent caesarean section under spinal anaesthesia. Each group received subarachnoid block with rapid administration of crystalloid fluid (co loading). The patients' characteristics like age, height, weight and ASA were similar and no significant difference was observed between the groups as shown in Table 1. The distribution of hypotension was similar in both the groups and was with p value > .05 (42% in group E and 43% in group P). Although there was rise in heart rate from baseline value till ten minutes in both the groups, statistically significant difference was found between the two groups at 4 minutes (97.6 ± 10.9 in group E and 101.4 ± 7.7 in group P) which was clinically insignificant (p value < 0.05). The systolic blood pressure dropped down from the baseline value till five minutes intra-operatively in both the groups and thereafter, it was steadily rising, but these changes were statistically not significant when compared at their corresponding time intervals between the groups except at 1,2,3 minutes (p value < 0.05). The diastolic blood pressure dropped down from the baseline value till five minutes intra-operatively in both the groups and thereafter, a steady rise was observed and these changes were statistically not significant when compared at their corresponding time intervals between the groups except at 2 minutes was 72 ± 9.3 mm Hg in group E and 75.14 ± 4.7 in group P (p value = 0.007) and 4 minutes (p value = 0.04). The mean blood pressure dropped down from the baseline value till four minutes intraoperative in both the groups and thereafter it was steadily rising and these changes were statistically not significant when compared at their corresponding time intervals between the groups except at 2 minutes ($P=0.03$) (Figure 1). There was statistically significant difference in the oxygen saturation at 15 minutes intraoperative which is

clinically insignificant (Figure 2). Apgar score of the baby at birth, 1st minute and 5th minute in both the groups did not predict any significant statistical difference as shown in Table 2. Although pH changes in group E (7.2 ± 0.06) and group P (7.38 ± 0.04) are statistically significant ($P=0.002$) but there was no true foetal acidosis in either groups ($pH < 7.2$). Vasopressor requirement among the two groups was statistically significant ($p < 0.05$) which was 4.8 ± 5.6 mg in group E and 92 ± 112 mg in group P.

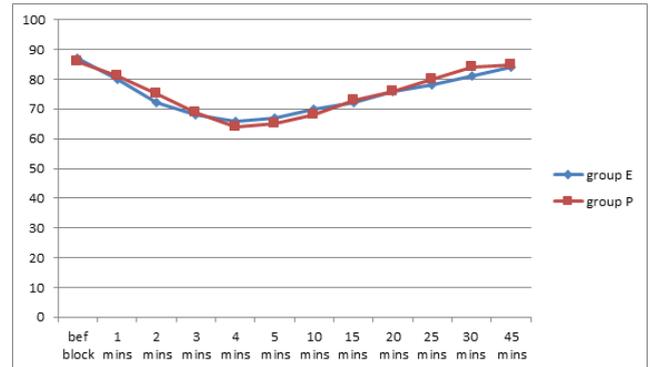


Fig. 1: Showing distribution and comparison of Mean Arterial BP (mmHg) between two groups Group E: Ephedrine Group P: Phenylephrine

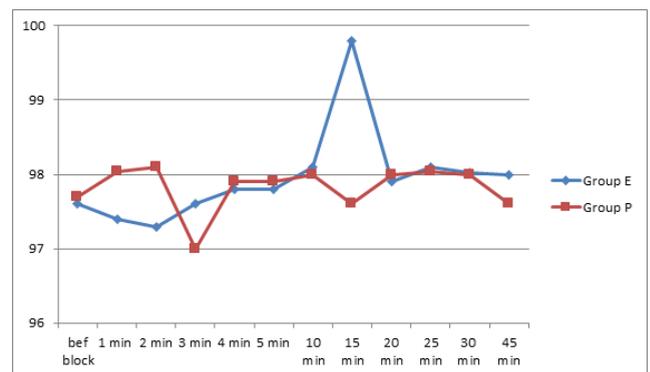


Fig. 2: Showing distribution of Oxygen Saturation (percentage) in two groups Group E: Ephedrine Group P: Phenylephrine

4. Discussion

In our study, the insignificant variations in the weight, height, age as well as ASA status of the parturients between the groups, emphasize the fact that the present study was made blind on the weight, height, age and ASA of the parturients. In other words, parturients considered for our study who received ephedrine 6mg or phenylephrine 100 mcg were more or less similar as regards their age, weight, and height and ASA status on the study of comparison of the two drugs. In our study, the incidence

Table 1: Demographic profile of the study participants

Parameters	Group E (n=50)	Group P (n=50)	Degree of freedom	P value & Inference
Age in years (mean±SD)	26.6±2.25	27.7±2.1	98	0.63(NS)
Weight in Kgs (mean±SD)	61.9±5.25	71.4±6.97	98	0.30(NS)
Height in Cms (mean±SD)	160.4±5.58	157.6±4.81	98	0.30(NS)
ASA (I:II)	39:1	36:4	1	0.35(NS)

(p>0.05; Not Significant), Group E: Ephedrine, Group P: Phenylephrine

Table 2: Apgar score of the children born at birth, 1 min and 5mins of delivery

Time points	Group E	Group P	p value
At birth	7.44±0.5	7.38±0.5	0.8
1 min	8.52±0.7	8.64±0.6	0.24
5 mins	8.7±0.6	8.64	0.1

(p>0.05; Not Significant), Group E: Ephedrine, Group P: phenylephrine

of hypotension was 42% in both group E and group P without any statistical difference when we used crystalloid co-loading. M Khan et al. observed a difference ($p < 0.0008$) in hypotension incidence between coload (44%) and preload (70%) groups which is comparable with the present study.¹³ In a landmark trial conducted by Dyer the effect of coload with Crystalloid in hypotension was studied.¹⁴ In this trial 50 patients undergoing caesarean section were randomized to receive 20 mL/kg Ringer lactate solution IV either by coload or preload (20 min before the anesthesia). The incidence of hypotension was significantly decreased in the coload versus preload group (36% vs 60%) and ephedrine requirements before delivery were also reduced (median: 0 vs 10 mg). A slightly different design was followed in a study conducted by NganKee et al where the authors compared coload with no fluid with infusion of phenylephrine in both groups.¹⁵ The group which received coload with fluids showed decrease in the incidence of hypotension from 28% to 2% and the dose of Phenylephrine required in coload group was also significantly less. The less efficacy of the preload was because of the rapid redistribution. There are several studies which shows reduction in incidence of hypotension with preloading too.

In both the group, heart rate was kept near baseline value until the induction of anesthesia after which heart rate increased significantly for about ten minutes parallel to interval of fall in mean arterial pressure. Following which the heart rate was back to base line values in both the group. Heart rate was similar in ephedrine group and the phenylephrine group at all measured intervals. However, at 4 to 5 minutes interval, the heart rate was at the range of 95-100 beats per minute in group E and 100-105 beats per minute in group P, which are statistically significant ($p < 0.05$) though clinically not significant. Similar findings were found by M Khan et

al who observed heart rate changes with increased trend for around ten minutes. This change was attributed to causes like anxiety, aortocaval compression and hypotension. The difference in the incidence of hypotension between the groups was statistically not significant ($P > 0.05$). The difference in systolic blood pressure between two groups after delivery at all times except at 2, 3 minutes was statistically insignificant ($P > 0.05$). At the 2 minute, the range of systolic blood pressure in two groups was 98-102 mmHg ($P = 0.001$), 3 minutes systolic blood pressure was 90-95 mmHg ($P = 0.04$). The difference in diastolic blood pressure between two groups after delivery at all times except at 2, 4 minutes was statistically insignificant ($P > 0.05$), at 2 mins the diastolic blood pressure was 54-63 mmHg ($P = 0.007$) and at 4 minutes diastolic blood pressure was 50-55 mmHg ($P = 0.04$). The difference in mean blood pressure between two groups after delivery at all times except at 2 minutes was statistically insignificant ($P > 0.05$), at 2 minutes mean blood pressure was 70-75 mmHg ($P = 0.03$). These findings were in accordance with the results of the studies conducted by M Khan et al and Nazir I et al.^{13,16}

In our study, the average vasopressor consumption is reduced in ephedrine group compared to the phenylephrine group i.e. Group E- 4.8±5.6 mg and Group P- 92 ± 112 µg ($P = 0.0001$), assuming the equivalent dose of ephedrine and phenylephrine was 6 mg and 100 µg respectively, which is statistically significant. The incidence of fall in blood pressure was the maximum during the first 10 minutes following subarachnoid block and we observed that vasopressor used was maximum in this period. This corresponds to the immediate sympathetic block after intrathecal injection. We also observed that phenylephrine was used more frequently by 10 minutes compared to ephedrine. It is readily apparent by the wider standard deviations of mean systolic blood pressure values in the phenylephrine group but there was no statistical

significant difference ($p > 0.05$). Statistical hemodynamic difference at 2 to 5 minutes between the groups was observed, but clinically not important heart rate and blood pressure were within normal limits in both the groups. In our study, there was significant higher incidence of bradycardia in group which received phenylephrine (0/50 vs 15/40: group E vs group P; $p = 0.021$) which can be explained by the α -agonist action with resultant reflex bradycardia. However, this was responsive to injection glycopyrolate without adverse consequences. The result of this study were in accordance with the studies of Lee et al (RR of 4.79; 95% CI, 1.47–15.60) and Nazir I et al (5/50 vs 17/50 in phenylephrine group) with $p < 0.05$. On the other hand, the incidence of nausea and vomiting also more in phenylephrine group than ephedrine group 9/50 (18%) vs. 10/50 (20%) in our study, which was not statistically significant ($P = 0.16$).^{16,17} Our study did not find any difference in the efficacy between the two groups of ephedrine and phenylephrine in decreasing the incidence of hypotension. The results of this study was similar to the study conducted by Nazir et al and Adigun et al.^{16,18}

In our study the two groups had no difference in birth weight of neonates ($P > 0.05$). Mean neonatal umbilical cord pH in group E was 7.2 ± 0.06 and group P was 7.37 ± 0.04 with p value 0.002 which was statistically significant. The umbilical cord pH was higher in the group with phenylephrine when compared to the other group but there was no difference in the incidence of fetal acidosis between the two groups. This was similar to the study conducted by Prakash et al, Nazir I et al, Cooper et al.^{16,18,19} Our study results was contradicting the results of the study done by Ngankee et al and AnnaLee et al where the umbilical artery pH was less in neonates in ephedrine group than phenylephrine group.^{15,17} Changes in the umbilical cord acidity indirectly shows evidence of uteroplacental insufficiency and hence from our results we can tell that uterine blood flow is better in phenylephrine group. But Apgar score was similar in both groups at 1 or 5 minutes. There was no significant difference in birth weight between two groups. Limitations in the present study are that it did not do loading for all the parturients, lacking preload group or control group to compare the incidence of hypotension. Hypotension due to blood loss and experience of the operating surgeon in controlling bleeding might also be a confounding factor. Block height was not equal in all the patients. We took only unpaired umbilical cord blood sample.

We conclude that ephedrine 6 mg and phenylephrine 100 μ g did not have difference in the efficacy to manage hypotension during spinal anaesthesia for caesarean delivery. However, maternal bradycardia was more in the phenylephrine group. The incidence of fetal acidosis and neonatal status of the babies were the same in both groups.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare no conflict of interest.

References

- Miseljic N, Basic E, Miseljic S. Causes of an Increased Rate of Caesarean Section. *Mater Socio-Medica*. 2018;30:287–9.
- Birnback DJ, Browne IM. Anesthesia for Obstetrics. vol. Vol. 2. 7th ed. Miller RD, Elsevier UCL, editors. Philadelphia, USA: Churchill Livingstone Elsevier; 2010. p. 2203–40.
- Harada MY, Ko A, Barmparas G, Smith EJ, Patel BK, Dhillon NK, et al. 10-Year trend in crystalloid resuscitation: Reduced volume and lower mortality. *Int J Surg*. 2017;38:78–82.
- Wang X, Xu JM, Zhou F, He L, Cui YL, Li ZJ. Maternal position and development of hypotension in patients undergoing cesarean section under combined spinal-epidural anesthesia of intrathecal hyperbaric ropivacaine. *Med Sci Monit*. 2015;21:52–8.
- Chooi C, Cox JJ, Lumb RS, Middleton P, Chemali M, Emmett RS, et al. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev*. 2020;1(7):CD002251.
- Rijs K, Mercier FJ, Lucas DN, Rossaint R, Klimek M, Heesen M. Fluid loading therapy to prevent spinal hypotension in women undergoing elective caesarean section: Network meta-analysis, trial sequential analysis and meta-regression. *Eur J Anaesthesiol*. 2020;37:1126–42.
- Xu C, Liu S, Huang Y, Guo X, Xiao H, Qi D. Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis. *Int J Surg*. 2018;60:48–59.
- Lee JE, George RB, Habib AS. Spinal-induced hypotension: Incidence, mechanisms, prophylaxis, and management: Summarizing 20 years of research. *Best Pract Res Clin Anaesthesiol*. 2017;31:57–68.
- Bajwa SJ, Kulshrestha A, Jindal R. Co-loading or pre-loading for prevention of hypotension after spinal anaesthesia! a therapeutic dilemma. *Anesth Essays Res*. 2013;7:155–9.
- Riley ET, Mangum K, Carvalho B, Butwick AJ. The Crystalloid Co-Load: Clinically as Effective as Colloid Preload for Preventing Hypotension from Spinal Anaesthesia for Caesarean Delivery. *Turk J Anaesthesiol Reanim*. 2019;47:35–40.
- Hennebry MC, Stocks GM, Belavadi P, Barnes J, Wray S, Columb MO, et al. Effect of i.v. phenylephrine or ephedrine on the ED50 of intrathecal bupivacaine with fentanyl for caesarean section. *Br J Anaesth*. 2009;102:806–11.
- Atashkhoaie S, Pourfathi H, Naghipour B, Meshgi S. The Effect of Prophylactic Infusion of Combined Ephedrin and Phenylephrine on Maternal Hemodynamic after Spinal Anesthesia for Cesarean Section: A Randomized Clinical Trial. *Iran J Med Sci*. 2018;43:70–4.
- Khan M, Nisai W, Farooqi A, Ahmad N, Qaz S. Crystalloid Co-Load: A Better Option Than Crystalloid Pre-Load For Prevention Of Postspinal Hypotension In Elective Caesarean Section. *Internet J Anaesthesiol*. 2013;32(1):1–8.
- Dyer RA, Farina Z, Joubert IA, Toit PD, Meyer M, Torr G, et al. Crystalloid preload versus rapid crystalloid administration after induction of spinal anaesthesia (coload) for elective caesarean section. *Anaesth Intens Care*. 2004;32:351–7.
- Ngankee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anaesthesia for caesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. *Anaesthesiology*. 2005;103:744–50.
- Nazir I, Mubasher AB, Qazi S, Velayat NB, Showkat AG. Comparison between phenylephrine and ephedrine in preventing hypotension during spinal anesthesia for cesarean section. *J Obstet Anaesth Crit Care*. 2012;2:92–7.

17. Lee A, Ngankee WD, Gin T. Dose response meta- analyses of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anaesthesia for elective caesarean delivery. *Anesth Analg.* 2004;98:483–90.
18. Adigun TA, Amanor-Boadu SD, Soyannwo SD. Comparison of intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during elective caesarean section under spinal anaesthesia. *Afr J Med Med Sci.* 2010;39:13–20.
19. Cooper DW, Carpenter M, Mowbray P, William RD, Ryall DM, Manmohan SK. Fetal and maternal effects of phenylephrine and ephedrine during spinal anaesthesia for caesarean delivery. *Anesthesiology.* 2002;97:1582–90.

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