Original Article

OPEN ACCESS

Comparison of Phenylephrine infusion vs Nor-epinephrine Infusion on Maternal Hemodynamics and Neonatal Outcomes During Elective Lower Segment Caesarean Section under Sub-Arachnoid Block

Shahid Khan[1], Zil Maurij Fiaz[2], Muhammad Haroon Anwar[3], Rana Imran Sikander[4], Ahmad Ali[5], Kiran Ayesha[6]

[1]Associate Professor,[2] House Officer, [3] Resident Anesthesia,[4] Professor of Anesthesia, [5] Resident Anaesthesia,[6]Assisstant Professor

[2]Department of Medicine, Pakistan Institute of Medical Sciences, Islamabad, [5]Lady Reading Hospital, Peshawar, [1,3,4,6]Department of Anesthesiology and Critical Care Medicine, Pakistan Institute of Medical Sciences, Islamabad,

Author`s Contribution

[1,3]Substantial contributions to the conception or design of the work; or the acquisition, [3]Final approval of the version to be published [4,5]Drafting the work or revising it critically for important intellectual content, [2,6]Active participation in active methodology, critical review

Funding Source: None
Conflict of Interest: None

Received: Dec 9, 2023
Accepted: Feb 28, 2024

Address of Correspondent
Dr. Shahid Khan
Associate Professor
Department of Anesthesiology and Critical Care Medicine,
Pakistan Institute of Medical Sciences, Islamabad
shahidkhan1974@gmail.com

ABSTRACT

Objective: To compare the efficacy of Phenylephrine and Nor-epinephrine IV infusions in maintaining maternal hemodynamics during EL-LSCS.

Methodology: This randomized control trial study was conducted department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad from March, 2023 to November, 2023. This study enrolled 62 patients fulfilling the inclusion criteria i.e., patient of age 18-45 years undergoing elective LSCS under SAB were enrolled in the study. While those having hypertension, pre-clampsia, eclampsia, pre-existing bradycardia, fetal distress and hypersensitivity to the medications used in the study were excluded. Enrolled patients were divided into two groups using computer generated random numbers with Group N patients received Nor-epinephrine infusion at rate of 2.5 Mcg/min while Group P patients received phenylephrine infusion at rate of 50 Mcg/min. Intraoperatively maternal hemodynamics were monitored and infusions were titrated to effect. Neonatal outcomes were assessed using APGAR score with umbilical cord ABGS carried out if clinically indicated.

Results: Group P patients had statistically significant lower mean heart rate at 5,10,15 and 20 minutes as compared to group N. Similarly, pressures were significantly higher in group P than group N at 5,10,15,20 and 25 minutes. This required frequent changes in the rate of Phenylephrine infusion with the desired effect being achieved after 25 minutes of induction of Sub-Arachnoid block.

Conclusion: Low dose Nor-Epinephrine infusion is safe and provides a better hemodynamic profile during Caesarean Section.

Keywords: Sub-Arachnoid Block, Spinal Anesthesia, Post Spinal Hypotension, Caesarean Section, Phenylephrine, Nor-epinephrine.

Cite this article as: Khan S, Fiaz ZM, Anwar MH, Sikander RI, Ahmad A, Ayesha K. Comparison of Phenylephrine infusion vs Nor-epinephrine Infusion on Maternal Hemodynamics and Neonatal Outcomes During Elective Lower Segment Caesarean Section under Sub-Arachnoid Block. Ann Pak Inst Med Sci. 2024; 21(1):74-79. doi. 10.48036/apims.v20i1.919.

Introduction

Lower segment Caesarean Section (LSCS) is a frequently performed operation. The rate of LSCS is on the rise in Pakistan. The rate of baby delivery through LSCS was 3.2% in 1990-91 while it rose to 19.6% in 2017-18.[1] LSCS can be performed as an elective procedure as well as an emergency procedure depending upon the indication and condition of mother and the neonate. The procedure can be carried out under regional or general anesthesia. For obstetric patients undergoing LSCS provision of safe general anesthesia can be challenging. There are a number of anesthetic concerns such as upper airway edema, more fragile upper respiratory tract mucosa, increased incidence

of difficult airway, greater risk of desaturation and aspiration.[2] Considering these factors regional anesthesia provides a suitable and safe alternative to General anesthesia.[3] Regional anesthesia for LSCS can be provided either in the form of Sub-Arachnoid Block (SAB), Epidural anesthesia or Combined Spinal Epidural Anesthesia (CSE). Most commonly LSCS is performed under SAB.[4] SAB commonly known as spinal anesthesia involves injection of local anesthetic in the sub-arachnoid space by means of spinal needle. Spinal anesthesia provides rapid onset of symmetrical dense block allowing surgery to start earlier than epidural anesthesia. Furthermore, SAB provides effective post operative analgesia.[4] One of the side effects of neuraxial block is sympathectomy leading to hypotension. The incidence of severe hypotension is high as 40%.[5] Hypotension can lead to uteroplacental insufficiency and thus can cause fetal hypoxia and acidosis. This ultimately leads to potential adverse fetal outcomes such hypoxic ischemic encephalopathy, cerebral palsy and other neurological sequalae[6]. Therefore, in order to improve both maternal and fetal outcomes, sub-arachnoid block induced hypotension should be prevented and if it occurs should be managed appropriately. This involves the use of intravenous fluid boluses and vasopressor agents.

However, in pregnancy, fluid boluses are less efficient in preventing hypotension associated with neuraxial blockade due to plasma volume expansion [7]. Therefore, vasopressors seem to be an ideal choice to prevent and manage maternal hypotension. There are number of vasopressors available. Most commonly employed vasopressors include phenylephrine and nor-epinephrine. Phenylephrine which is alpha 1 agonist is considered to be a gold standard in managing maternal hypotension.

However important side effect of phenylephrine is bradycardia.[8] This limits its potential use. Another vasopressor of interest is Nor-epinephrine. This drug acts on both beta- and alpha-adrenergic receptors and is therefore is not associated with bradycardia.[9] Furthermore, Norepinephrine which was once thought to be safe if only given through central line. It can now be given from peripheral intravenous access without causing any significant side effects particularly if low concentration of drug is infused for a short period of time. [10-11] Recent studies have shown that intermittent IV bolus dose of diluted Nor-epinephrine is effective in managing post-spinal hypotension and has a relatively lower incidence of bradycardia.[12-15] However very limited literature is available regarding use of Nor-epinephrine infusion during EL-LSCS carried out under SAB. Some studies show that nor-epinephrine infusion is superior to phenylephrine infusion in managing maternal hypotension and causes less bradycardia.[16-17]

Our Single Blind Randomized Control Trial aims to compare the efficacy of norepinephrine infusion with phenylephrine infusion in maintaining maternal hemodynamics during elective lower segment Caesarean section, focusing on maternal side effects.

Methodology

After approval from Ethical Review Board, this single-blind randomized control trial based was carried out department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad from March, 2023 to November, 2023. The total sample size was 62 which was calculated according to WHO calculator by taking level of significance 5%, power of test to be 80% and P1= 0.048 and P2= 0.317).[18] Patients fulfilling the inclusion criteria i.e., patient of age 18-45 years undergoing elective LSCS under SAB were enrolled in the study. While those having hypertension, pre-eclampsia, eclampsia, pre-existing bradycardia, fetal distress and hypersensitivity to the medications used in the study were excluded. Those patients in whom after induction of SAB, block level was found to be lower than T4 upon testing to cold stimulus were excluded from the study. Enrolled patients were divided into two groups using computer generated random numbers. During surgery Group N patients received Nor-epinephrine infusion at rate 2.5 Mcg/min while Group P patients received phenylephrine infusion at rate of 50 Mcg/min. The infusions were titrated to effect.

Upon arrival in the OR; pre-operative assessment was reviewed, NPO status was confirmed, standard ASA monitoring was attached. Sub-arachnoid block given at L3-L4 interspace using 12.5 mg of Hyperbaric bupivacaine. Group N patients received nor-epinephrine infusion which was started at the time of administration of local anesthetic in the sub-arachnoid space while Group P received phenylephrine infusion. Infusions were given through 18G peripheral IV line placed in the ante-cubital vein. The infusion site was continuously monitored for any extravasation or surrounding tissue edema or injury. Intra-operatively NIBP, HR, SpO2, ECG were monitored every 5 minutes till the end of surgery. Baby after delivery was assessed using APGAR score by the pediatrician and umbilical cord ABGs were carried out if indicated. Infusions started at the time of induction of SAB were

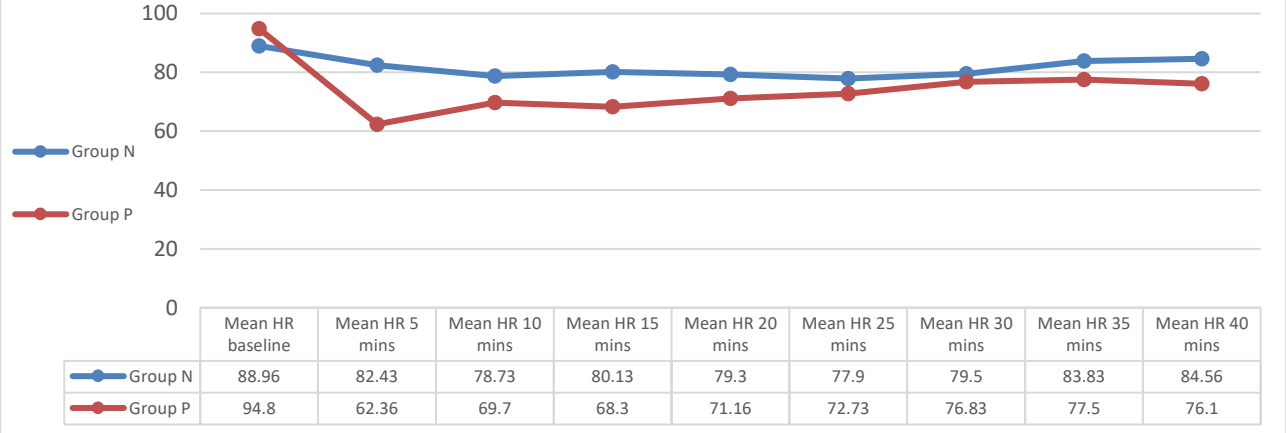
doi. 10.48036/apims.v20i1.919

continued in the post-operative recovery area under the observed of senior anesthetist. They were slowly tapered and stopped over first hour of patient stay in the recovery.

Results

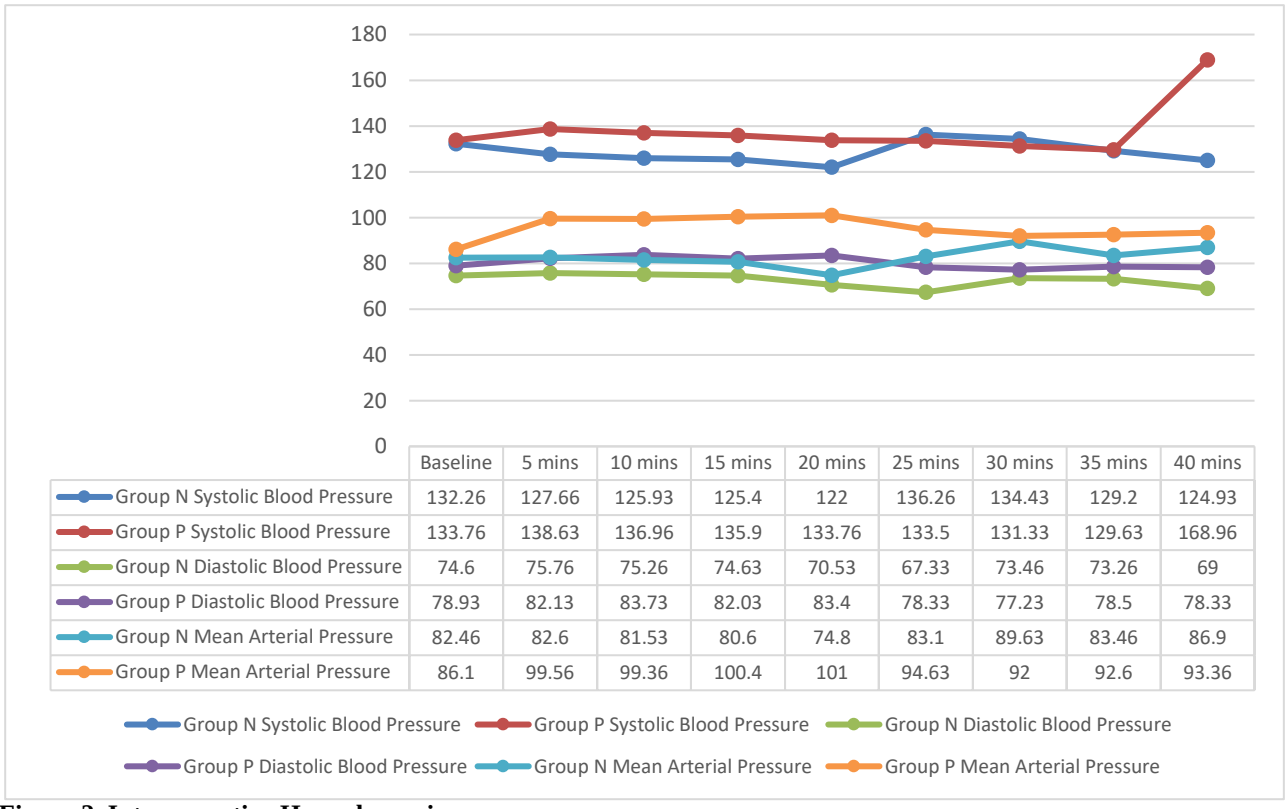
Mean age was comparable among both groups. Patients belonging to Group N had a mean age of 32.63 ±5.15 years. While in group P mean age was 32.70 ± 5.71 years. All the patients belonged ASA II class. None of the patients included in the study had any co-morbid. Baseline Mean Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial pressure were comparable in both groups with p values being greater than 0.05 for each variable. The trend of intra-operative Heart Rate is shown in figure 1.

By applying independent sample t-test a significant difference in heart rate was observed among both groups at 5,10,15 and 20 minutes. The p value observed at these intervals were lower than 0.05. The heart rate at these points of time were significantly lower in Group P as



	Mean HR baseline	Mean HR 5 mins	Mean HR 10 mins	Mean HR 15 mins	Mean HR 20 mins	Mean HR 25 mins	Mean HR 30 mins	Mean HR 35 mins	Mean HR 40 mins
Group N	88.96	82.43	78.73	80.13	79.3	77.9	79.5	83.83	84.56
Group P	94.8	62.36	69.7	68.3	71.16	72.73	76.83	77.5	76.1

Figure 1. Intraoperative Heart Rate.



	Baseline	5 mins	10 mins	15 mins	20 mins	25 mins	30 mins	35 mins	40 mins
Group N Systolic Blood Pressure	132.26	127.66	125.93	125.4	122	136.26	134.43	129.2	124.93
Group P Systolic Blood Pressure	133.76	138.63	136.96	135.9	133.76	133.5	131.33	129.63	168.96
Group N Diastolic Blood Pressure	74.6	75.76	75.26	74.63	70.53	67.33	73.46	73.26	69
Group P Diastolic Blood Pressure	78.93	82.13	83.73	82.03	83.4	78.33	77.23	78.5	78.33
Group N Mean Arterial Pressure	82.46	82.6	81.53	80.6	74.8	83.1	89.63	83.46	86.9
Group P Mean Arterial Pressure	86.1	99.56	99.36	100.4	101	94.63	92	92.6	93.36

Figure 2. Intraoperative Hemodynamics.

compared to Group N requiring adjustment of phenylephrine infusion.

The intra-operative trend of Systolic blood pressure, Diastolic blood pressure and mean arterial pressure is shown in figure 2.

Statistically significant hemodynamic variations between the two groups were seen at different points of time. SBP, DBP, MAP was significantly higher in group P as compared to group N at 5,10,15,20 minutes intervals (p-values <0.05). DBP and MAP were also significantly higher at 25 minutes (p-value <0.05). However, in group N all hemodynamic variables were close to baseline following induction of anesthesia. No episode of hypotension requiring a bolus dose of vasopressor was observed in both groups. No extravasation or cannulation site injury was noted in both groups.

APGAR score was comparable among both groups. Group N having mean APGAR score of 8.4± 0.49 at 1 minutes and 9.8± 0.40 at 5 minutes. Mean APGAR score at 1 minutes for Group P was 8.13 ± 0.97 while at 5 minutes it was 9.40 ± 0.49.

Discussion

This study provides an insight regarding optimal control of hemodynamics during LSCS being carried out under SAB. Spinal anesthesia is associated with sympathectomy which causes hypotension and hypoperfusion body tissues including placenta. There by it adversely affects maternal and fetal outcomes. In pregnancy this hypotension is less responsive to IV fluid boluses as the patient already has her plasma volume expanded. Furthermore, excessive crystalloid boluses can lead to interstitial edema which compromises tissue oxygenation and causes gut ileus, post operative nausea and vomiting ultimately hampering post operative recovery.[19] As the cause of hypotension is sympathectomy leading to decreased peripheral vascular resistance. Therefore, it is better managed by use of vasopressors. This study compares IV Phenylephrine infusion with that of IV Nor-Epinephrine infusion in controlling hemodynamics while monitoring for adverse effects. Baseline hemodynamic variables were comparable in both groups. However, IV Nor-Epinephrine infusion provided better hemodynamic stability as compared to IV Phenylephrine infusion. The statistically significant difference was observed at 5 mins, 10 mins, 15 mins, 20 mins and 25 mins after induction of SAB. Mean Heart rate in phenylephrine group at these points of time were 62.36± 6.98, 69.70 ± 7.94, 68.30 ± 8.52, 71.16 ± 12.57, 72.27 ± 16.54. While at these time intervals mean Heart rate in group N was 82.43 ± 9.33, 78.73 ± 9.1.6, 80.13 ± 7.25, 79.30 ± 5.37, 77.90 ± 5.42. Apart from 25 minutes time interval, p-value was less than 0.05. This indicates the Heart rate was significantly lower in group P as compared to Group N. This is supported by a number of studies. A study conducted by Theodoraki K. et al shows that patients receiving Phenylephrine infusion had greater incidence of bradycardia 31.7% as compared to those receiving Nor-epinephrine infusion 4.8% with a value of less than 0.05.[18]

Standardized Heart rate over time was also significantly lower in patients receiving Phenylephrine infusion as compared to Nor-epinephrine infusion.[18] However, this study, Nor-epinephrine was infused at a rate of 4 Mcg/min while our study found that a lower rate of Nor-epinephrine infusion i.e., 2.5 Mcg/min is equally effective. Lower doses are thought to be associated with less extravasation and infusion site injury in a recent meta-analysis.[11]

Similarly in another study conducted the incidence of bradycardia was greater among patients receiving Phenylephrine infusion i.e., 43.3% as compared to 20% in Nor-epinephrine group. The patients in this study received Nor-epinephrine at a rate of 2.5 Mcg/min and Phenylephrine infusion at a rate of 50 Mcg/min. The difference in the incidence of bradycardia among two groups was statistically insignificant which is contrary to our study[16]. Similarly, results were seen in other studies, where incidence of bradycardia was greater among patients receiving Phenylephrine infusion as compared to Nor-epinephrine infusion.[17,20,21] Furthermore, in our study the SBP, DBP and MAP were significantly greater in group P as compared to group N at 5,10,15 and at 20 minutes time interval with a p-value of less than 0.05.

MAP and DBP were also significantly higher in group P as compared to group N with a p-value of less than 0.05. Higher pressures and associated bradycardia at these time frames frequently required adjustment of rate of infusion of Phenylephrine. The duration of action of Phenylephrine given as an IV bolus is 15-20 minutes.[8] Thus, one can easily infer that adjustment of rate of infusion of Phenylephrine will achieve the targeted hemodynamics after a period of a period of time rather than instantaneously. However, Nor-epinephrine half-life is 2.4 minutes thus adjusting its infusion rate can achieve targeted outcomes earlier[9]. On the other hand, in the Nor-epinephrine group although pressures were lower than group P at 5,10,15,20 and 25 minutes but they were close to their baseline values thus requiring no adjustment in the infusion rate of Nor-epinephrine. In literature available

pressures were comparable among patients receiving Phenylephrine infusion and those receiving Nor-Epinephrine infusion.[12,13,15-17] The difference can be due to demographic difference in study population as well difference in drug quality. APGAR score was comparable among two groups and this is supported by a number of studies indicating that fetal outcomes are comparable among two groups. [12,13,15-17]

Conclusion

Low dose Nor-Epinephrine infusion at a rate 2.5 Mcg/min provides better hemodynamic profile during EL-LSCS under SAB which is safe and a better alternative to Phenylephrine infusion.

Limitation of study: The study provides no information regarding effect of these vasopressor infusion on mother and baby in case of LSCS as well those suffering from hypertensive disorders of pregnancy. Further studies are needed in these subset of patient population.

References

1. Amjad A, Imran A, Shahram N, Zakar R, Usman A, Zakar MZ, Fischer F. Trends of caesarean section deliveries in Pakistan: secondary data analysis from Demographic and Health Surveys, 1990-2018. BMC Pregnancy Childbirth. 2020;20:753. https://doi.org/10.1186/s12884-020-03457-y
2. Butterworth JF, Mackey DC, Wasnick JD, editors. Morgan & Mikhail's clinical anesthesiology. Seventh edition. New York: McGraw Hill; 2022.
3. Hines R, Jones S. Stoelting's anesthesia and co-existing disease. 8th ed. Philadelphia: Elsevier, Inc; 2021.
4. Thompson JP, Moppett IK, Wiles M, editors. Smith and Aitkenhead's textbook of anaesthesia. Seventh edition. Edinburgh: Elsevier; 2019.
5. Fakherpour A, Ghaem H, Fattahi Z, Zaree S. Maternal and anaesthesia-related risk factors and incidence of spinal anaesthesia-induced hypotension in elective caesarean section: A multinomial logistic regression. Indian J Anaesth. 2018;62:36. https://doi.org/10.4103/ija.IJA_416_17
6. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ. 2010;340:c1471-c1471. https://doi.org/10.1136/bmj.c1471
7. Pascual ZN, Langaker MD. Physiology, Pregnancy [Internet]. StatPearls Internet. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559304/.
8. Phenylephrine (systemic): Drug information [Internet]. UpToDate. 2023. Available from: https://www.uptodate.com/contents/phenylephrine-systemic-drug-information?search=phenylephrine&source=panel_search_result&selectedTitle=1~139&usage_type=panel&showDrugLabel=true&display_rank=1.
9. Norepinephrine (noradrenaline): Drug information [Internet]. UpToDate. 2023. Available from: https://www.uptodate.com/contents/norepinephrine-noradrenaline-drug-information?search=norepinephrine&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F202407.
10. Richardson CP, Noonan MA, McHughs SM. Administering Norepinephrine Peripherally Is Safe, as Long as There Is No IV Extravasation. Anesth Analg. 2021;132:e80-e81. https://doi.org/10.1213/ANE.0000000000005461
11. Liu L, Luo L, Li L, Jin M. Safety of high-concentration norepinephrine for peripheral intravenous use. Comment on Br J Anaesth.2021;127:e135-e137. https://doi.org/10.1016/j.bja.2021.07.004
12. Puthenveettil N, Sivachalam S, Rajan S, Paul J, Kumar L. Comparison of norepinephrine and phenylephrine boluses for the treatment of hypotension during spinal anaesthesia for caesarean section - A randomised controlled trial. Indian J Anaesth. 2019;63:995. https://doi.org/10.4103/ija.IJA_481_19
13. Mohta M, Dubey M, Malhotra RK, Tyagi A. Comparison of the potency of phenylephrine and norepinephrine bolus doses used to treat post-spinal hypotension during elective caesarean section. Int J Obstet Anesth. 2019;38:25-31. https://doi.org/10.1016/j.ijoa.2018.12.002
14. Tiwari JP, Verma SJ, Singh AK. A Prospective Randomized Study Comparing the Bolus Doses of Norepinephrine and Phenylephrine for the Treatment of Spinal Induced Hypotension in Cesarean Section. Cureus [Internet]. 2022 [cited 2023 Dec 6]; https://doi.org/10.7759/cureus.27166
15. Patil A, Chavan R, Mudalagirigowda SK, Adda S. A Comparative Study to Evaluate the Effect of Norepinephrine and Phenylephrine in the Treatment of Post Spinal Hypotension for Caesarean Section. Arch Anesth Crit Care. 2022; https://doi.org/10.18502/aacc.v8i1.8240
16. Singh J, Singh J, Mitra S, Anand L, Goel B, Kaur M. Comparison of prophylactic phenylephrine and norepinephrine infusion on umbilical arterial pH and maternal blood pressure during spinal anaesthesia for caesarean delivery. Indian J Anaesth. 2022;66:115. https://doi.org/10.4103/ija.ija_345_21
17. Goel K, Luthra N, Goyal N, Grewal A, Taneja A. Comparison of norepinephrine and phenylephrine infusions for maintenance of haemodynamics following subarachnoid block in lower segment caeserean section. Indian J

Anaesth.2021;65:600. https://doi.org/10.4103/ija.IJA_185_21

18. Theodoraki K, Hadzilia S, Valsamidis D, Stamatakis E. Prevention of hypotension during elective cesarean section with a fixed-rate norepinephrine infusion versus a fixed-rate phenylephrine infusion. A double-blinded randomized controlled trial. Int J Surg. 2020;84:41-49. https://doi.org/10.1016/j.ijsu.2020.10.006
19. Hardman JG, Hopkins PM, Struys MMRF, editors. Oxford textbook of anaesthesia. Oxford: Oxford University Press; 2017.p1042. https://doi.org/10.1093/med/9780199642045.001.0001
20. Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, Shapiro RE, Ranganathan P. An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. Int J Obstet Anesth. 2017;29:18-25. https://doi.org/10.1016/j.ijoa.2016.08.005
21. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, Carvalho JCA. Comparison of Intermittent Intravenous Boluses of Phenylephrine and Norepinephrine to Prevent and Treat Spinal-Induced Hypotension in Cesarean Deliveries: Randomized Controlled Trial. Anesth Analg. 2019;129:1312-1318. https://doi.org/10.1213/ANE.0000000000003704