COMPARISON BETWEEN TWO DIFFERENT DOSES OF NOREPINEPHRINE INFUSION FOR PREVENTING POST SPINAL ANESTHESIA HYPOTENSION DURING CESAREAN SECTION

Rupak Bhattarai[1], Amarendra Kumar Yadav[2], Parasmani Shah[3], Prabin Sharma[4],*

Affiliation

1. *Associate Professor/ Deapartment of Anesthesiology, Nobel Medical College Teaching Hospital, Nepal*
2. *Consultant/ Department of Anesthesiology, Nobel Medical College Teaching Hospital, Nepal*
3. *Lecturer/ Deapartment of Anesthesiology, Nobel Medical College Teaching Hospital, Nepal*
4. *Junior Resident/ Deapartment of Anesthesiology, Nobel Medical College Teaching Hospital, Nepal*

ARTICLE INFO

Received : 14 February, 2023

Accepted : 08 July, 2023

Published : 10 November, 2023

ORA 350

DOI : https://doi.org/10.3126/bjhs.v8i2.59851

Corresponding Author

Dr. Rupak Bhattarai

Associate Professor

Deapartment of Anesthesiology

Nobel Medical College Teaching Hospital, Nepal

Email: bhattarairupak@hotmail.com

ORCID : https://orcid.org/0000-0002-5521-081X

Citation

Comparison between two different doses of Norepinephrine infusion for preventing post spinal Anesthesia Hypotension during Cesarean section, Rupak Bhattarai, Amarendra Kumar Yadav, Parasmani Shah, Prabin Sharma. BJHS 2023;8(2)21. 2014-2018.

ABSTRACT

Introduction

Post spinal maternal hypotension is common complication during cesarean section. Norepinephrine is a vasopressor recently used in obstetrics anesthesia. However, there are less data available regarding its optimal dose.

Objective

The main objective of this study is to compare two doses of infusion of norepinephrine for post spinal hypotension during cesarean delivery.

Methodology

A prospective, randomized, double blinded study on full term pregnant patient scheduled for elective cesarean delivery. The infusion of Norepinephrine started after spinal anesthesia after patient randomly divided into two groups. Group A received norepinephrine infusion rate of 0.025ug/kg/min and Group B received at rate of 0.050ug /kg/min. The norepinephrine was continued till 5 minutes after the delivery of fetus and subsequently stopped. These two groups were compared with systolic blood pressure, mean arterial pressure, heart rate, intraoperative hypotensive episodes, Nausea and Vomiting, tachycardia and neonatal outcomes.

Result

Systolic blood pressure and mean arterial pressure was higher in group B when compared with group A at all time intervals intraoperatively. The minimum systolic blood pressure and mean arterial blood pressure in group A were 91.61±8.76 and 59.8±5.29 and group B were 90.67±1.21 and 65±3.46 respectively. No significant difference in heart rate between the two groups. In 0.025ug/kg/min group had 23 (46%) hypotensive episode whereas in 0.050ug/kg/min group had 6 (12%) hypotensive episodes ($p<0.001$). In group A 9 patient had nausea and vomiting. Bradycardia was seen in 2 % of patient in group A. Tachycardia was seen in 4% of patients in group B. Apgar score was comparable and significant ($P<0.05$) in 10 minutes.

Conclusion

In the present study, the infusion of 0.050ug/kg/min norepinephrine reduced the hypotensive episodes when compared with the infusion of 0.025ug/kg/min norepinephrine following spinal Anesthesia during cesarean delivery.

KEY WORDS

Apgar score, Cesarean, Norepinephrine, Post spinal hypotension

INTRODUCTION

Spinal anesthesia is the choice of technique commonly used in today's world for cesarean section. However, hypotension is the common complication that occurs with spinal anesthesia.[1] The prolonged hypotension generally leads to diminish in uteroplacental blood flow and fetal acidosis.[2-4] In today's practice the most commonly and appropriate used vasopressor is phenylephrine in cesarean section. But, use of phenylephrine may cause severe bradycardia and decrease in cardiac output. On the other hand, the use of ephedrine leads to maternal tachycardia, increase incidence of maternal nausea and vomiting and alterations in fetal PH.[5,6] There are some recent studies which showed that the Norepinephrine leading to increase in heart rate and cardiac output due to mild and dose dependent B-adrenergic effects to counteract the vasoconstriction properties and therefore maintaining the blood pressure and heart rate during spinal anesthesia for cesarean section.[7,8] Moreover, these recent studies have shown that norepinephrine could be an alternative to phenylephrine in terms of maintaining the blood pressure and heart rate for cesarean section with spinal anesthesia. But different studies done recently does not show the optimal dose of infusion of norepinephrine. So, the main objective of this study is to find out the appropriate dose of infusion of norepinephrine with two different regimens for preventing hypotension during cesarean section following spinal anesthesia.

METHODOLOGY

A prospective, randomized, controlled double blind study was planned. It was conducted on 100 parturient. Approval of this study was obtained from Nobel Medical College Teaching Hospital ethical committee and informed consent was obtained from the recruited mother for the procedure. The study was conducted from November 2021 to October 2022 at Nobel Medical College Teaching Hospital, Biratnagar, Nepal. The randomization was done by computer generated online random number generator. The codes of the patient were kept as a sequential numbered sealed envelope by the anesthesiologist who was not responsible for patient management in this study. The anesthesia junior resident who was not involved in the study was assigned for opening the envelope and preparing the drug as written in each envelope.

The inclusion criteria for this study includes age group of 17 years to 40 years planned for elective cesarean section, singleton, full term pregnancy, ASA I and ASA II. The exclusion criteria for this study include Patient with medical co-morbidities (Diabetes Mellitus, CVS disease, severe anaemia, pre-eclampsia and eclampsia and coagulopathy), baseline systolic blood pressure (SBP) less than 100 mmHg, emergency caesarean section, body mass index above 40kg/m2, ASA III –ASA IV.

Routine pre anesthetic check (PAC) up was done one day prior to surgery as for elective cases. All patients received of inj. Metoclopramide 10mg and inj. Ranitidine 50mg two hours prior to operation intravenously as per protocol lay down by department of Anesthesiology of our institution.

In the preparation room/operation room:

- Baseline non invasive systolic, diastolic, mean arterial pressure was recorded
- Heart rate was recorded
- Peripheral oxygen saturation was recorded
- Continuous ECG recording
- Placement of 18G cannula and IV drip with Ringer Lactate.

With the patient in sitting position, a 25-Gauge Quincke needle was inserted at L3-4 or L4-5 interspinous space and 0.5% heavy bupivacaine 2.2ml was injected intrathecally after ascertaining the free flow of cerebrospinal fluid (CSF).

After the subarachnoid block patients were divided in 2 groups;

1. Group 1: 0.025ug/kg/min received 5 ug norepinephrine bolus followed by norepinephrine infusion in a starting dose of 0.025 ug/kg/min.
2. Group 2: 0.050ug/kg/min received 5 ug norepinephrine bolus followed by norepinephrine infusion in a starting dose of 0.050 ug/kg/min.

The bolus dose of norepinephrine was given soon after subarachnoid block was achieved. The norepinephrine infusion was continued 5 minutes after the delivery of fetus and stopped subsequently.

The patients were kept in supine position with left uterine displacement after spinal anesthesia. Non invasive blood pressure (NIBP), Mean arterial pressure (MAP), Heart rate (HR), Pulse oximetry (SPO2) were recorded as baseline. Systolic blood pressure (SBP) and mean arterial pressure (MAP) were recorded at every one-minute interval for 6 readings and then every 2.5 minutes for next 4 readings and then at 5 minutes interval till 5 minutes after delivery of the fetus. Heart rate (HR) was recorded as baseline and in every 2.5 minutes interval. Level of blocks was checked by cotton swab soaked in sprit and surgery was allowed once the level extended up to T6-T8. Patient in whom hypotension [defined as 20% reduction from baseline systolic blood pressure (SBP) or any reduction of MAP to < 50mmHg] developed was treated by IV bolus doses of inj. ephedrine 3mg. If maternal bradycardia, it was managed with injection Atropine 0.6 mg intravenous bolus.

After delivery of fetus injection oxytocin 5 IU was injected as a single bolus dose, followed by 10 IU infusion at the rate of 30 drops per minute. Total blood loss was recorded at the end of surgery. Neonatal condition was assessed by APGAR score 1, 5 and 10 minutes after the delivery.

The primary outcome of this study was to find the frequency of post spinal hypotension. The secondary outcomes included systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR), frequency of intraoperative nausea and vomiting, intraoperative requirements of ephedrine and atropine, Apgar score at 1, 5 and 10 minutes after the delivery.

Statistical analysis: Data were collected and entered in master chart in MS Excel using SPSS 17.0 (statistical package

for social science). Categorical data were calculated as percentage. Descriptive data were interpreted as mean (SD) and median wherever required. All variable was analyzed using different statistical test (Independent t Test and chi-squared test) as needed, P value <0.05 interpreted as statistically significant.

Sample size

The sample size was taken as 100 patients with 50 in each group with previous study[9] and by using the formula:

$n = \frac{2(z\alpha+z\beta)^2 S^2}{d^2}$ Za = 1.96 at 95 % confidence level, Zb= 0.84 at 80% power

RESULTS

The demographic characteristics of the two groups are reported in Table 1.

Table 1: Demographic characteristics of the study population

Parameters	GROUP A	GROUP B	P value
Age	24.98±3.55	24.58±4.22	0.610
Weight	63.56±6.78	60.28±5.87	0.011

The values are in mean (±) SD. P-value < 0.05 is considered to be significant.

Table 2: Baseline mean hemodynamic variables

Parameters	GROUP A (n=50)	GROUP B (n=50)	P-value
SBP (mmHg)	119.72±9.10	120.32±8.88	0.739
DBP (mmHg)	72.32±7.22	69.80±5.65	0.055
MAP (mmHg)	88.12±7.01	86.64±6.12	0.264
HR/min	89.04±14.04	88±9.71	0.66

The values are in means (±) SD. P- value < 0.05 is considered to be significant. SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, MAP= Mean Arterial Pressure, HR=Heart Rate

Table 3: Comparison of SBP between the groups

Time (Min)	SBP GROUP A	SBP GROUP B	P- value
0	122±9.47	127.62±7.71	0.002
1	118.18±9.43	123.60±7.80	0.002
2	111.56±9.20	121.96±8.25	<0.05
3	107.86±14.65	121.34±8.76	<0.05
4	108.00±10.59	121.80±8.57	<0.05
5	113.82±8.75	121.80±10.12	<0.05
7.5	115.74±7.26	121.48±9.51	0.001
10	117.04±8.39	122.08±6.95	0.002
12.5	115.93±8.30	123.56±6.03	<0.05
15	117.31±7.90	124.41±7.15	0.001
20	118.12±6.10	124.00±8.13	0.047
25	119.86±8.07	130.00±7.07	0.236

The values are in means (±) SD. P- values <0.05 is considered to be significant.

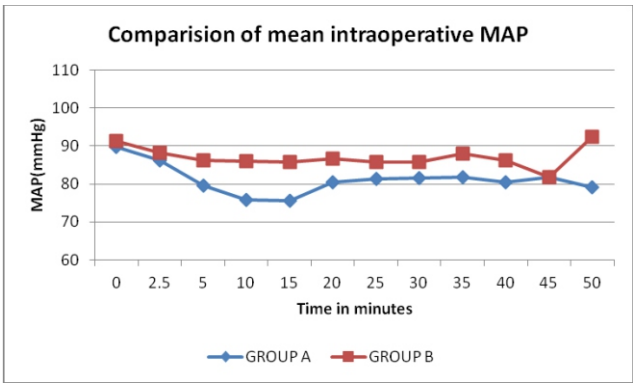

Figure 1: Comparison of mean intraoperative MAP

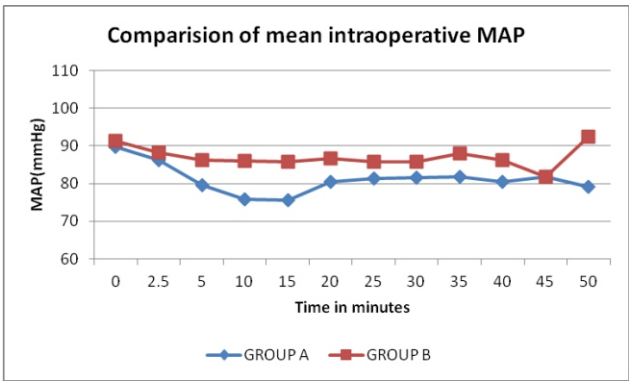

Figure 2: Comparison of mean intraoperative Heart Rate

The values of mean of HR of each group was plotted in figure 2. The graph shows no significant difference in HR between the two groups.

Table 4: Hypotensive episodes after SAB

Hypotension	GROUP A (n=50)	GROUP B (n=50)	P-value
Number of patients(n)	23 (46%)	6 (12%)	0.001
Time of occurrence(minutes)	13.26 ± 4.15	15 ± 6.32	0.546
Minimum SBP(mmHg)	91.61±8.76	90.67±1.21	0.623
Minimum DBP(mmHg)	44.04±4.76	52.17±4.95	0.008
Minimum MAP(mmHg)	59.89±5.29	65±3.46	0.015

P- values <0.05 is considered to be significant. SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP= Mean Arterial Pressure

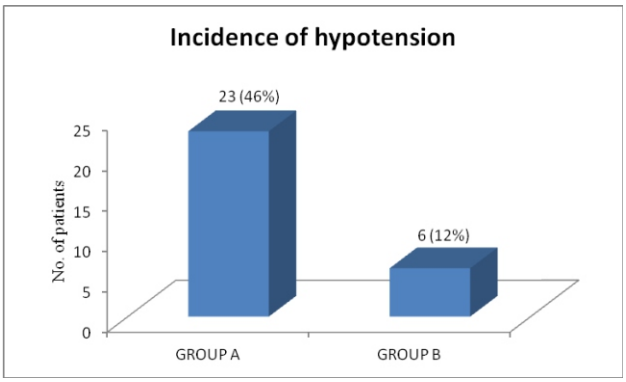

Figure 3: Incidence of hypotension

The table 8 shows the side effects encountered in both the groups during the study. The overall incidences of the side effects were nausea (14%), vomiting (4%), bradycardia (2%),

tachycardia (4%), and hypertension (2%). Intraoperatively 7 parturient in each group perceived nausea, and 2 parturient in group A and 7 parturient in group B had vomiting. All women who develop nausea and vomiting were treated with IV ondansetron 4mg. In group B (2%) developed bradycardia. All were treated with IV atropine 0.6mg. Tachycardia was seen in 4% in group A and 2% in group B.

Table 5: Side effect observed in both the groups during the study

Side effects	GROUP A (n=50)	GROUP B (n=50)	Total (n=100)
Nausea	7(14%)	0	7(14%)
Vomiting	2(4%)	0	2(4%)
Bradycardia	0	1(2%)	1(2%)
Tachycardia	2(4%)	1(2%)	3(6%)
Hypertension	0	1(2%)	1(2%)

The values are in frequency and percentage.

Table 6: Comparison of APGAR score

APGAR	GROUP A	GROUP B	P- value
1 minute	7.10±.30	7.00±.00	0.022
5 minute	8.60±.49	8.34±.51	0.012
10 minute	9.12±.38	8.76±.43	<0.05

The values are in means (±) SD. P- values <0.05 is considered to be significant.

DISCUSSION

Different studies recommends that aortocaval compression prevents venous return and therefore sympathetic block leads to venous pooling in the lower limbs to synergistically reduce venous return, decreasing cardiac output and causing maternal hypotension.[10,11] The decrease of systemic vascular resistance secondary to small artery vasodilation with some degree of venous dilatation is main effect of Spinal anesthesia.[12-14]

Thus, in present days Ephedrine, phenylephrine and Norepinephrine are three commonly used vasopressors during cesarean delivery under spinal anesthesia. Therefore, we thought to compare the appropriate dose of Norepinephrine infusion for preventing post spinal hypotension during cesarean section.

In the present study the mean age in Group A and Group B were 24.98±3.55 years and 24.58±4.22 years respectively. Similarly, the mean weight in Group A and Group B were 63.56±6.78 kg and 60.28±5.87 kg respectively. Our study showed both the groups were comparable with regard to age and weight.

We compared two doses of Norepinephrine infusion 0.025ug/kg/min and 0.050ug/kg/min during cesarean delivery, one being lower dose whereas other being an intermediate dose. Similarly, Ahmed M. Hasanin et al[15] compared three doses for norepinephrine infusion during cesarean section 0.025ug/kg/min, 0.05ug/kg/min and 0.75ug/kg/min and suggested 0.05ug/kg/min being the best dose for norepinephrine infusion during cesarean delivery.

Norepinephrine during spinal anesthesia for maintaining blood pressure during cesarean section had been recently reported first by Ngan Kee et al.[16] As cesarean delivery being performed in every hospital and the main challenge is to prevent the post spinal hypotension, therefore there are lots of new guidelines and protocols being added day by day. Ngan Kee et al [17] recently advocated a study where he used Norepinephrine infusion ranged between 1.25ug/min and 5 ug/min and concluded that Norepinephrine group had a lower incidence of hypotension when compared with controlled group. Though our study was limited only to norepinephrine group and didn't compare with any control group.

In the present study, the systolic blood pressure (SBP) decreased in both groups in 1 and 2 minutes when compared with baseline, but after that SBP was static in group B through- out the operation whereas it was in decreasing traits in group A. Ngan kee et al[17]also showed that using infusion of 5ug/ml of norepinephrine infusion was more effective in maintaining the blood pressure thus decreasing the incidence of hypotension which was similar finding in our study.

In our study, there was no major reduction of heart rate when compared between the two groups. One patient in group B had bradycardia which was treated with injection atropine. Two patients in group A had tachycardia whereas one patient in group B had tachycardia which settled by its own as it was transient. Similarly, the study done by A.H Hasanin et al [15] found that bradycardia requiring atropine was seen in 4.3% cases in 0.025ug/kg/min group, 3.2% cases in 0.05ug/kg/min group and 7.3% cases in 0.075ug/kg/min. Though we didn't study 0.075ug/kg/min infusion group, the other two groups finding were 2% cases had bradycardia in 0.05ug/kg/min and none in 0.025ug/kg/min group in our study.

The incidence of hypotension when compared between two groups in our study, it was found that 46% of patient had hypotension in group A whereas only 6% of patient in group B. Ngan kee et al [17] also had a similar finding to our study that infusion of 5ug/ml norepinephrine was effective in decreasing the incidence of hypotension. Another study by Corke et al [18]and Wei et al[9] also reported the incidence of hypotension in 0.050ug/kg/min infusion group but the incidence of hypotension was much higher in their studies.

Nine patients in 0.025ug/kg/min group had Nausea and Vomiting in our study and this may be due to central hypotension seen more in this group.

Apgar score in context to neonatal wellbeing were compared in both the groups. Though APGAR score was higher in group A compared to group B it was statistically not significant except in 10min score.

CONCLUSION

The infusion of 0.050ug/kg/min norepinephrine effectively reduced the episode of post spinal hypotension when compared with infusion of 0.025ug/kg/min during cesarean delivery.

LIMITATIONS OF THE STUDY

Further studies may be needed as number of patients in our study were less. The possible bias might arise as norepinephrine were manually prepared; it would be better if computer control infusion were made. The study would be stronger if compared with more norepinephrine infusion doses, as we only compared the two doses of norepinephrine.

ACKNOWLEDGEMENTS

We would like to Sincerely thanks to all my patients, my residents, obstetrics team, colleagues who assisted to make this study possible.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

FINANCIAL DISCLOSURE

None

REFERENCES

1. 1. Klöhr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand. 2010 Sep;54(8):909-21. PMID: 20455872
2. N. Fratelli, F. Prefumo, S. Andrico, A. Lorandi, D. Recupero, G. Tomasoni, T. Frusca, Effects of epidural analgesia on uterine artery Doppler in labour, BJA: British Journal of Anaesthesia, Volume 106, Issue 2, February 2011, Pages 221–224. DOI: 10.1093/bja/aeq317
3. Valentin M, Ducarme G, Ceccaldi PF, Bougeois B, Luton D. Uterine artery, umbilical, and fetal cerebral Doppler velocities after epidural analgesia during labor. Int J Gynaecol Obstet. 2012 Aug;118(2):145-8. PMID: 22613492
4. C. Antoine and B. K. Young, "Fetal lactic acidosis with epidural anesthesia," American Journal of Obstetrics & Gynecology, vol. 142, no. 1, pp. 55–59, 1982. DOI: 10.1016/S0002-9378(16)32284-0
5. Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg. 2010 Nov;111(5):1230-7. PMID: 20841418
6. Anusorntanawat R, Uerpairojkit K, Thongthaweeporn N, Charuluxananan S. Safety of Phenylephrine in Antihypotensive Treatment during Spinal Anesthesia for Cesarean Section. J Med Assoc Thai. 2016 Feb;99(2):188-96. PMID: 27249899
7. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology. 2015 Apr;122(4):736-45. DOI: 10.1097/ALN.0000000000000601
8. Hiltebrand LB, Koepfli E, Kimberger O, Sigurdsson GH, Brandt S. Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. Anesthesiology. 2011 Mar;114(3):557-64. DOI: 10.1097/ALN.0b013e31820bfc81
9. Wei C, Qian J, Zhang Y, Chang X, Hu H, Xiao F. Norepinephrine for the prevention of spinal-induced hypotension during caesarean delivery under combined spinal-epidural anaesthesia: Randomised, double-blind, dose-finding study. Eur J Anaesthesiol. 2020 Apr;37(4):309-315. DOI: 10.1097/EJA.0000000000001152
10. Marx GF. Supine Hypotension Syndrome During Cesarean Section. JAMA. 1969;207(10):1903–1905. DOI:10.1001/jama.1969.03150230117018
11. HOLMES F. Spinal analgesia and caesarean section; maternal mortality. J Obstet Gynaecol Br Emp. 1957 Apr;64(2):229-32. DOI: 10.1111/j.1471-0528.1957.tb02626.x.
12. Sharwood-Smith G, Drummond GB. Hypotension in obstetric spinal anaesthesia: a lesson from pre-eclampsia. Br J Anaesth. 2009 Mar;102(3):291-4. DOI: 10.1093/bja/aep003
13. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure and cardiac output monitoring during cesarean delivery: a randomized, double-blind comparison of low-dose versus high-dose spinal anesthesia with intravenous phenylephrine or placebo infusion. Anesthesiology. 2008 Nov;109(5):856-63. DOI: 10.1097/ALN.0b013e31818a401f
14. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, Greenwood J, James MF. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology. 2009 Oct;111(4):753-65. DOI: 10.1097/ALN.0b013e3181b437e0
15. Hasanin AM, Amin SM, Agiza NA, Elsayed MK, Refaat S, Hussein HA, Rouk TI, Alrahmany M, Elsayad ME, Elshafaei KA, Refaie A. Norepinephrine Infusion for preventing Post spinal Anesthesia Hypotension during cesarean Delivery: A Randomized Dose-finding Trial. Anesthesiology. 2019 Jan; 130(1):55-62. DOI: 1097/ALN.0000000000002483
16. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. Anesthesiology. 2015 Apr;122(4):736-45. DOI: 10.1097/ALN.0000000000000601
17. Ngan Kee WD, Lee SWY, Ng FF, Khaw KS. Prophylactic Norepinephrine Infusion for Preventing Hypotension During Spinal Anesthesia for Cesarean Delivery. Anesth Analg. 2018 Jun;126(6):1989-1994. doi: 10.1213/ANE.0000000000002243. Erratum in: Anesth Analg. 2019 Apr;128(4): e60. PMID: 28678073
18. Corke BC, Datta S, Ostheimer GW, Weiss JB, Alper MH. Spinal anaesthesia for Caesarean section. The influence of hypotension on neonatal outcome. Anaesthesia. 1982 Jun;37(6):658-62. DOI: 10.1111/j.1365-2044.1982.tb01278.x