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Original Research Article

Comparison of Efficacy of two Different Doses of Glycopyrrolate Pretreatment on Hemodynamics Changes Associated with Phenylephrine Infusion During Cesarean Section Under Spinal Anaesthesia

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Abstract

Background and aims:

Phenylephrine infusion is the drug of choice for hypotension following spinal anaesthesia in caesarean section but is associated with a dose related reflexive slowing of maternal heart rate (HR) and a corresponding decrease in Cardiac output. **Methods:** A prospective, randomized study was performed on 60 parturients (30 in each group), undergoing elective caesarean section. All parturients were administered SAB with 2.2ml of 0.5% bupivacine (hyperbaric) in left lateral position and phenylephrine infusion was started at the rate of 50µg/min. Parturients were randomly allocated to receive either 0.1mg (group G1) or 0.2 mg glycopyrrolate (group G2) intravenously with the start of infusion. The maternal systolic blood Pressure (SBP) and HR were recorded every 5 min till delivery of baby (taken at clamping of cord). **Results:** Neither of the groups had significant hypotension but HR and SBP were better maintained in group G1 than G2 while the change in SBP from the baseline SBP was significantly higher in G2 up till 20 min ($p<0.05$). There were no episodes of nausea and vomiting, and the level of spinal blockade achieved was similar in both the groups. The umbilical cord pH was higher in group G1 as compared to group G2, but the Apgar score was similar in both the groups. **Conclusion:** Pretreatment with 0.1 mg glycopyrrolate maintains better haemodynamics and fetal umbilical pH as compared to 0.2mg when given with phenylephrine infusion.

Keyword: Phenylephrine infusion, Glycopyrrolate, Hypotension, Hemodynamics changes

Introduction

Hypotension is one of the commonest complications when administering spinal anaesthesia in caesarean section. It leads to cerebral hypo-perfusion and activation of vomiting center in mother.[1] while, the reduction in uteroplacental blood flow can cause fetal acidosis, hypoxia and neurological injuries.[1,2] Vasopressor infusion along with rapid crystalloid

cohydration is the modality of choice for preventing hypotension.[3] Phenylephrine and ephedrine are commonly used vasopressors. Ephedrine increases blood pressure (BP) by increasing cardiac output (CO) via stimulation of cardiac β_1 receptors but decreases fetal pH, base excess and umbilical artery oxygen content [3,4,5,6,7] Phenylephrine is an α receptor agonist without β adrenergic receptor activity and reduces the risk of hypotension [3,4, ,6,7,8,9] and fetal acidosis.[3,10] However, its use is often associated with a dose related reflexive slowing of maternal HR and a corresponding decrease in CO.[8,9,10,11] Glycopyrrolate is a quaternary ammonium anticholinergic drug which does not affect fetal heart rate or heart rate variability since it does not penetrate placental barriers in significant amounts.[12,13,14,15] The decrease in CO due to reflex decrease in HR caused by phenylephrine infusion can be attenuated or prevented by using glycopyrrolate along with phenylephrine infusion.[12,13]

This study was undertaken with the aim to evaluate the efficacy of two different doses of glycopyrrolate on hemodynamic changes associated with use of phenylephrine infusion for prevention of hypotension in cesarean section under spinal anaesthesia with regards to, maternal hemodynamic changes as measured by SBP and HR, and fetal outcome as measured by Umbilical artery blood gas analysis and Apgar score of the newborn.

Methods and Materials:

After institutional review board approval, this study was conducted in the Department of Anesthesiology and Intensive Care, Maulana Azad Medical College and associated hospitals, New Delhi, in parturients admitted for elective caesarean section. It was a randomized double-blind study on parturients with singleton, term pregnancy scheduled for elective caesarean delivery under spinal anaesthesia. Parturients associated with pregnancy induced hypertension, cardiovascular disease, cerebrovascular disease, renal impairment, known fetal abnormality, allergy to any study medication, taking monoamine oxidase inhibitors or tricyclic antidepressants and height <140 or >180cmwere excluded from the study. The primary objective of the study was to measure maternal SBP and HR every 5 minutes after spinal anaesthesia till delivery of baby, Apgar score of baby at 1 min&5 min and Umbilical artery blood gas analysis of new born.

Since there was no previous similar study, taking the study by Kee Ngan et al[10] who studied the same parameters taking a sample size of 30 patients in each group, we took 60 subjects (30 in each group).All parturients was randomly (computer generated random number table) allocated to receive 0.1 mg or 0.2 mg glycopyrrolate:

Group G1 (n=30): All parturients in this group was administered 0.1mg of glycopyrrolate. Group G2 (n=30): All parturients in this group was administered 0.2mg of glycopyrrolate.

Anesthetic Technique:

A prospective, randomized study was performed on 60 parturients (30 in each group), undergoing elective caesarean section. After overnight fasting, the parturients were taken to the OT and baseline NIBP and HR were recorded. Co-hydration was started at rate of 100 ml/hr of Ringer's lactate and spinal anaesthesia was administered with the parturient in left lateral position. After confirmation of free flow of cerebrospinal fluid (CSF), 2.2 ml of hyperbaric bupivacaine 0.5% (w/v) was injected intrathecally, along with the intrathecal administration, glycopyrrolate was injected i.v as per drug allocation. An investigator who was not involved in patient care or assessment prepared the study solutions.

Group G1: parturients received pretreatment with glycopyrrolate 0.1mg diluted in saline to 2ml intravenously.

Group G 2: parturients received pretreatment with glycopyrrolate 0.2mg diluted in saline to 2ml intravenously

Coloading was administered to a maximum of 1 liter over 15 minutes after which the flow was reduced to maintenance rate at 100 ml/hr. The SBP, DBP and HR were recorded at 5 minutes interval until delivery. The level of sensory block was assessed using response to pin prick. Phenylephrine infusion was prepared by careful dilution in 5% dextrose solution and administered through infusion pump in a 50-ml syringe. The infusion rate was initially at a fixed rate of 30ml/h (50µg/min) at the in both groups and later was titrated to maintain SBP according to the following algorithm that is derived from study by Ngan kee et al empirically[16]:

- Infusion rate (ml/h) = (10 - error %) × 3

Where error% = (measured SBP – baseline SBP)/baseline SBP× 100.

The infusion rate was maintained within 0 to 60 ml/h (0 to 100µg/min) and continued till the delivery of baby. Blood pressure was maintained between 80% to 120% of baseline. Hypotension (defined as SBP <80% of baseline) was managed by increasing the infusion of the drug till SBP was within 80-120% of baseline. Similarly, Hypertension (defined as SBP >120% of baseline) was managed by decreasing the infusion according to the formula till SBP is within defined limits. Any episode of bradycardia (defined as HR <60 beats/min) was recorded and managed by administration of glycopyrrolate in incremental doses of 0.2mg till a HR of 60beats/min was attained. The infusion regimes in both groups were continued until delivery (to be taken at clamping of cord) after which the study was terminated and the attending anesthesiologist was allowed to continue management as per patient requirement. After delivery, Apgar scores of the neonate were assessed by a pediatrician at 1 and 5 min after delivery. Samples of umbilical arterial (UA) blood were collected from a double-clamped segment of umbilical cord and analyzed immediately. The randomization code was not revealed until the surgery was over.

Results

Table 1: Comparison of mean SBP within the group and between the groups:

Comparison of SBP in G1 from baseline (n=30)				Comparison of SBP in G2 from baseline (n=30)			Mean SBP G1 Vs G2
Time interval	**(SBP in mm Hg) Mean ± SD**	**Mean difference from baseline ± SD**	**p value**	**(SBP in mm Hg) Mean ± SD**	**Mean difference from baseline ± SD**	**p value**	**p Value**
Baseline	120.60 ± 7.80			122.57 ± 5.61			0.267
0 min	119.57 ± 12.34	1.033 ± 12.732	0.660	126.30 ± 11.92	3.733 ± 12.337	0.108	0.036
5 min	123.87 ± 16.76	3.267 ± 14.341	0.222	137.37 ± 21.74	14.8 ± 21.557	0.001	0.009
10 min	125.70 ± 15.69	5.1 ± 16.736	0.106	137.03 ± 20.42	14.207 ± 19.646	0.001	0.020
15 min	123.71 ± 14.11	3 ± 14.724	0.362	133.77 ± 16.56	11.192 ± 16.334	0.002	0.032
20 min	124.88 ± 7.95	5.375 ± 14.841	0.340	137.31 ± 15.62	13.385 ± 15.381	0.009	0.052
25 min	128.25 ± 9.57	8.75 ± 10.012	0.179	130.50 ± 17.62	5 ± 14.72	0.546	0.830
30 min	–			124.50 ± 0.71	2 ± 7.071	0.758	–

Table 2: Comparison of mean DBP within the group and between the groups:

Comparison of DBP in G1 from baseline (n=30)				Comparison of DBP in G1 from baseline (n=30)			Mean SBP G1 Vs G2
Time interval	(DBP in mm Hg) Mean ± SD	Mean difference from baseline ± SD	p value	(DBP in mm Hg) Mean ± SD	Mean difference from baseline ± SD	p value	p Value
Baseline	78.87 ± 5.61			81.17 ± 6.71			0.156
0 min	74.33 ± 10.14	-4.533 ± 9.183	0.011	82.13 ± 11.49	0.967 ± 12.848	0.683	0.007
5 min	81.00 ± 14.61	2.133 ± 14.197	0.417	85.83 ± 11.43	4.667 ± 12.012	0.042	0.159
10 min	78.27 ± 15.01	0.6 ± 15.106	0.829	86.00 ± 10.86	4.655 ± 11.89	0.044	0.028
15 min	77.57 ± 11.72	-0.905 ± 10.977	0.710	86.04 ± 12.30	4.808 ± 13.008	0.071	0.021
20 min	77.50 ± 9.67	-0.5 ± 14.273	0.924	84.46 ± 22.16	12.615 ± 22.329	0.064	0.056
25 min	78.75 ± 3.95	-0.5 ± 11.846	0.938	83.25 ± 16.52	0.25 ± 11.899	0.969	0.615
30 min	–			70.00 ± 9.90	-14 ± 18.385	0.476	–

Table 3: Comparison of mean HR within the group and between the groups:

Comparison of HR in G1 from baseline (n=30)				Comparison of HR in G1 from baseline (n=30)			Mean HR G1 Vs G2
Time interval	HR/min Mean ± SD	Mean difference from baseline ± SD	P value	HR/min Mean ± SD	Mean difference from baseline ± SD	P value	p Value
Baseline	90.63 ± 8.73			89.30 ± 9.76			0.579
0 min	99.10 ± 17.16	8.467 ± 12.182	0.001	101.10 ± 23.91	11.8 ± 19.372	0.002	0.711
5 min	84.50 ± 18.98	6.133 ± 18.188	0.075	97.77 ± 21.77	8.467 ± 20.826	0.034	0.015
10 min	87.90 ± 17.98	2.733 ± 17.538	0.400	93.34 ± 21.37	4.034 ± 22.075	0.333	0.293
15 min	72.38 ± 17.22	-1.762 ± 17.595	0.651	99.08 ± 18.95	9.077 ± 17.953	0.016	0.216
20 min	100.38 ± 21.11	9.5 ± 22.728	0.276	98.92 ± 15.03	6.333 ± 15.652	0.189	0.858
25 min	102.75 ± 15.76	13 ± 22.331	0.328	105.75 ± 7.23	11.75 ± 6.551	0.037	0.741
30 min	–			113.50 ± 4.95	21.5 ± 0.707	0.015	–

Table 4: Umbilical cord blood gas analysis

	Mean ± SD	Mean ± SD	P value
PH	7.33 ± 0.05	7.30 ± 0.05	0.018
SPO_2	39.13 ± 20.86	40.25 ± 20.72	0.835
PO_2	22.98 ± 7.13	23.94 ± 7.27	0.606
PCO_2	39.41 ± 7.21	40.74 ± 5.97	0.439
B.E	(-)4.46 ± 2.46	(-)5.00 ± 2.27	0.38
HCO_3	20.74 ± 3.10	20.39 ± 2.61	0.645

Table 5: Comparison of number of bolus of glycopyrrolate given to treat bradycardia between two groups BGLYCO- bolus of glycopyrrolate given)

BGLYCO	Group 1		Group 2		P Value
	Frequency	%	Frequency	%	
No	24	80.0%	27	90.0%	0.472
Yes	6	20.0%	3	10.0%	
Total	30	100%	30	100%	

Table 6: Comparison of total consumption of phenylephrine between two groups (CPHE in µg)

	Mean consumption in G1	Min-Max	Mean consumption in G2	Min-Max	P value
CPHE	**643.33 ± 324.23**	**200 – 1700**	**605.00 ± 414.68**	**150 – 2000**	0.691

The study was conducted on a total of 60 parturients with 30 parturient in each group.Both the groups were statistically comparable with regard to age, weight and height. The changes in maternal heart rate and blood pressure within groups was compared using ANOVA,

The mean baseline SBP was comparable between the two groups. The mean SBP and the change in SBP from the baseline SBP was significantly higher in group G2 compared to group G1. The Mean SBP at 0, 5, 10 and 15 min with p value of 0.036, 0.009, 0.020, 0.032 respectively and change in SBP from the baseline SBP at 5, 10, 15 and 20 min with p values of 0.001, 0.001, 0.002, and 0.009 respectively was significant in G2, while, in G1it was not significant at any of the measured time intervals. (Table1)

The mean baseline DBP was comparable between the two groups. The mean DBP at 0 min in group G1 was significantly lower from the baseline DBP (p value-0.011).

The mean DBP was significantly higher at 0, 10 and 15 min in G2 as compared to G1 with p values of 0.007, 0.028 and 0.021 respectively while, the change in mean DBP from the baseline values was statistically significantly higher at 5 and 10 min having p values of 0.042 and 0.044 respectively. (Table2). The DBP in both the groups were comparable at all other time intervals

The baseline heart rate was comparable between two groups. In group G1 the mean heart rate at 0 min was significantly higher from the baseline heart rate (P value- 0.001) but the change in mean heart rate with baseline values at 5, 10, 15, 20 and 25 min was not statistically significant. In G2, heart rate at 5 min was found to be significantly higher in group G2 as compared to group G1 and the change in heart rate at 0, 5 min and 15 min 25 min and 30 min was significantly higher from the baseline (p value-0.002, 0.034, 0.016, 0.037 and 0.015 respectively). (Table3).

Apgar scores at 1 and 5 minutes (mean value 9) in both the groups were similar and there was no significant difference found between the two groups.

The umbilical cord pH was found to be statistically significantly lower in the group G2 compared to group G1 (p value- 0.018).

Bolus glycopyrrolate of 0.2 mg was given for 6 episodes of bradycardia in 6 patients out of 30 patients in group G1 and in group G2 for 3 patients in group G2 out of 30 patients. This was statistically comparable between the two groups (p value - 0.472).

As shown in table6, the difference in total consumption of phenylephrine was not statistically significant between two groups (p value- 0.691).

Discussion

Hypotension is a common and serious side effect after SAB in parturients undergoing cesarean section with grave neonatal consequences i.e. fetal acidosis, hypoxia, neurological injuries and poor neonatal outcome.[1,2,8] Prevention of hypotension is better rather than treating it symptomatically to avert neonatal and maternal complications.[1,2,17,18] Combination of phenylephrine infusion along with cohydration is the modality of choice for management of hypotension. Faster onset and short duration of phenylephrine makes it administration by infusion more convenient, appropriate and effective.[19,20,21,22] A reflex decrease in heart rate is commonly encountered with phenylephrine use in clinical doses and may

require treatment with an anticholinergic.[2,10,12] This decrease in heart rate is associated with a significant reduction in cardiac output (CO). [23] It has been suggested that maternal cardiac output correlates closely with uteroplacental blood flow.[24] Thus, heart rate can be potentially used as surrogate marker for cardiac output and for guiding phenylephrine dosing.[9] Glycopyrrolate is an ideal drug that can compensate for CO reduction caused by phenylephrine infusion. However, there is limited literature on the appropriate doses of glycopyrrolate.[10] Different workers have used glycopyrrolate in doses varying from 0.2 mg bolus [10] to 4µg/kg [12] and found it to be effective in preventing bradycardia following phenylephrine infusion. Yoon et al found that use of glycopyrrolate 0.2 mg added to phenylephrine infusion to prevent hypotension by spinal anaesthesia was effective in maintaining heart rate and cardiac index.[10] Kee Ngan et al compared glycopyrrolate at dose of 4µg/kg and saline placebo along with phenylephrine infusion. Patients who received glycopyrrolate had a greater cardiac output, heart rate, similar stroke volume and lower median phenylephrine infusion rate compared with control. Number of patients who had one or more episode of hypertension was greater in the glycopyrrolate group, also glycopyrrolate group had greater cardiac output, greater heart rate and similar neonatal outcome in both the groups.[12] In our study, SBP maintained near base line value in group G1.Rise in SBP significantly greater from the baseline SBP in group G2 and from G1.Yoon et al, used a bolus of 0.2 mg glycopyrrolate with phenylephrine infusion (group- PG) and compared it with the phenylephrine infusion alone (group P). Significant differences in SBP compared to baseline value in each group and between the two groups. However cardiac index reduced significantly from 8 min to 15 min in group P compared to group PG. Our finding of SBP were different from the study done by Yoon et al.[10]

The baseline DBP was comparable between two groups (p value-0.156), as shown in table 2. The DBP in group G1 was significantly lower than the baseline line blood pressure at 0 min but subsequently returned to the base line blood pressure. While in group G2 it was significantly higher than baseline at 5 min and 10 min then after it also came near to the baseline. None of the studies has compared the DBP following use of phenylephrine infusion with glycopyrrolate. The parameters studied by them were cardiac output and SBP.

As shown in table 3, when compared within the groups, the mean baseline heart rate was comparable in both the groups (p value-0.579). The heart rate was significantly higher than baseline heart rate in group G2 at 0 ,5, 15, 25 and 30 min while it was significantly higher at only 0 min in group G1.But when compared between group at only 5 min the heart rate was significantly higher than group G1. The heart rate was maintained significantly near the baseline in group G1 compared to G2. Our finding of HR was similar to the study done by Kee Ngan et al and Yoon et al.[10,12] Yoon et al compared phenylephrine alone and combination of phenylephrine with glycopyrrolate at dose of 0.2 mg bolus found that heart rate was higher in glycopyrrolate group compared to phenylephrine alone.[10] Kee Ngan et al used combination of phenylephrine with glycopyrrolate at 4µg/kg and compared it with placebo. They found that glycopyrrolate group has higher heart rate and blood pressure from baseline value.[12]

Apgar scores

Apgar scores in the neonates in the two groups at 0 min and 5 min was 9 and 9 . There were no significant changes found in Apgar scores in both the group. Apgar scores have been found to be depressed in neonates where the mother has been

administered general anaesthesia and not under spinal anaesthesia.[25,26] Apgar scores have been found to be low when there is significant and persistent hypotension following SAB

Umblical Cord Blood Gas Analysis

It is now widely accepted that umbilical cord blood gas analysis can provide important information about the past, present and possibly the future condition of the infant. Hypotension decreases uteroplacental blood flow which in turn leads to fetal acidosis, hypoxia and neurological injuries. Sympathetic blockade reduces uteroplacental perfusion. The mean umbilical cord pH was significantly lower in group G2 than in group G1 (p value 0.018). However, pH in group G2 was comparable to other studies. Mean pH was reduced due to low pH in only one patient where surgery was prolonged. No other reason could be ascribed to this. Lower arterial cord pH may be associated with clinically significant outcome. Historically umbilical cord pH of 7.2 was considered as the lower limit of normal, but later it has been suggested that pH values of 7.02-7.18 represent the lower limit of normal umbilical artery pH. Significant adverse neonatal outcomes are rare with umbilical artery pH of more than 7.0.[27]

Total Consumption of Phenylephrine

The average consumption of phenylephrine was comparable between two groups (p value 0.691). The consumption of phenylephrine was less when used with glycopyrrolate as compared to phenylephrine alone as suggested by other studies. The consumption of phenylephrine was less when used with glycopyrrolate as compared to phenylephrine alone as suggested by Kee et al, Yoon et al, Stewart et al, Allen T et al.[6,7,10,12] In our study consumption of phenylephrine was less in both groups as compared with the studies done by Allen T[6] and Stewart et al [7]. In our study as we used glycopyrrolate in both the groups and the consumption of phenylephrine was comparable between two groups. The total dose of phenylephrine was similar to that used by other workers when they used phenylephrine with glycopyrrolate and was more when other workers used phenylephrine alone to maintain blood pressure.[6,7,10,12,15] The reason why the consumption of phenylephrine is less when used with glycopyrrolate may be due to the to the intrinsic property of glycopyrrolate to increase the blood pressure along with heart rate.[12,13,15]

Episodes Of Bradycardia

6patients developed bradycardia i.e. heart rate less than 60/min in group G1, while in group G2 total of 3 patients developed bradycardia. The incidence of bradycardia was comparable between two groups. Glycopyrrolate 0.2 mg stat was given in patients when they developed bradycardia in any group.A total 6 blouses was given in 6 patients i.e. one in each patients in group G1 and 3 boluses were given in 3 patients in G2 . After giving glycopyrrolate 0.2 mg bolus none of the patients developed bradycardia. There was no associated significant change in blood pressure, consumption of phenylephrine, Apgar score and pH of the neonatal umbilical cord in these parturients. This bradycardia might be due to baroreceptor reflex in response to phenylephrine consumption. One parturient had level of sensory blockade till at T3 and in this parturient the blood pressure was found to be 192 mm of Hg and heart rate reduced to 54 /min at 5 min. The infusion was stopped and glycopyrrolate bolus was given immediately. The cause of bradycardia in this parturient might be due to higher level of blockade along with reflex bradycardia due to phenylephrine. In a similar study by Kee Ngan et al the parturients who were pretreated with glycopyrrolate 4µg/kg along with phenylephrine infusion didn't show any episode of bradycardia.[12] Also in a study by Yoon et al who used 0.2 mg of

glycopyrrolate with phenylephrine infusion there was no episode of bradycardia.[10] In contrast to these studies 3 parturients in group G2 who had given 0.2 mg glycopyrrolate developed bradycardia and required 0.2 mg rescue boluses. We could not ascribe any reason of higher incidence of bradycardia in our study compared to the above studies. This aspect requires further investigation.

Episode of Nausea and Vomiting

Hypotension is the main cause of nausea and vomiting in parturients undergoing cesarean section under SAB. Hypotension leads to brain stem ischemia which activates vomiting center, it also releases emitogenic substances and causes nausea and vomiting. None of the parturients in both the groups developed nausea or vomiting during the course of surgery. This may be ascribed to preservation of blood pressure near baseline or higher. Our results were found to similar with Ure et al who found decreased incidence of nausea and vomiting with use of 200µg bolus of glycopyrrolate along with ephedrine for prevention of hypotension following SAB in parturients undergoing cesarean section.[13]

Conclusion:

This study was conducted to compare two different doses of glycopyrrolate i.e 0.1 mg (group G1) and 0.2 mg (group G2) for prevention of bradycardia during phenylephrine infusion during cesarean section under spinal anaesthesia To conclude: There was no difference in level of spinal blockade achieved between the two groups, hemodynamic parameters i.e. heart rate and SBP was better maintained in group G1 than G2,there was no episode of nausea and vomiting in both the groups as hypotension was not significant in either group, fetal outcome in terms of umbilical cord pH was higher in group G1 compared to group G2. This has significant fetal implications. As per international consensus there is insufficient evidence to recommend routine use of glycopyrrolate for prevention of hypotension.[28] Further work is required to identify an optimum dose for prophylactic bolus.

References:

1. Emmett RS, Cyna AM, Simmons SW.Techniques for preventing hypotension during spinal anaesthesia for caesarean section. The Cochrane Database of Systematic Reviews 2002, Issue 3.
2. Ngan Kee WD, Khaw KS. Vasopressors in obstetrics. What should we be using? Curr Opin Anaesthesiol 2006; 19:238–43.
3. Kobayashi S, Endou M, Sakuraya F, et al. The sympathomimetic actions of L-ephedrine and D-pseudoephedrine: direct receptor activation or norepinephrine release? Anesth Analg 2003; 97:1239–45.
4. Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anaesthesia for cesareandelivery.An effective technique using combination phenylephrine infusion and crystalloid cohydration. Anesthesiology 2005; 103:744–50.
5. Dyer RA, Reed AR, Van Dyk D et al. Hemodynamics effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anaesthesia for elective caesarean delivery. Anaesthesiology 2009; 111:753-65.
6. Allen TK, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anaesthesia for cesarean delivery. Anesth Analg 2010; 111:1221–9.
7. 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; 111:1230–7.

8. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. Cochrane Database Syst Rev 2006; CD002251.
9. Butwick AJ, Columb MO and Carvalho B. Preventing spinal hypotension during Caesarean delivery: what is the latest? Br J Anaesth 2015; 114 (2):183–6.
10. Yoon HJ, Cho HJ, Lee IH, Jee YS, Kim SM. Comparison of hemodynamic changes between phenylephrine and combined phenylephrine and glycopyrrolate groups after spinal anesthesiafor cesarean delivery. Korean J Anesthesiol 2012; 62:35–9.
11. Gupta S.Vasopressors and tight control of maternal blood pressure during caesarean delivery. J Anaesthesiol Clin Pharmacol 2013; 29(1): 1–3.
12. Ngan Kee WD, Lee SWY, Khaw KS, Ng FF.Hemodynamic effects of glycopyrrolate pretreatment before phenylephrine infusion during spinal anaesthesia for caesarean section. Int J Obstet Anesth 2013; 22:179–87.
13. Ure D, James KS, McNeill M, Booth JV. Glycopyrrolate reduces nausea during spinal anaesthesia for caesarean section without affecting neonatal outcome. Br J Anaesth 1999; 82:277–9.
14. Ali-Melkkila T, Kaila T, Kanto J, Iisalo E. Pharmacokinetics of glycopyrronium in parturients. Anaesthesia 1990; 45: 634-7.
15. Rucklidge MW, Durbridge J, Barnes PK, Yentis SM. Glycopyrronium and hypotension following combined spinal–epidural anaesthesia for elective caesarean section in women with relative bradycardia. Anaesthesia 2002; 57:4–8.
16. Ngan Kee WD, Lee SWY, Tan PE. Randomized double-blind comparison ofnorepinephrine and phenylephrine for maintenance of blood pressure during spinalanaesthesia for caesarean delivery. Anaesthesiology 2015; 122:736-45.
17. Wollman SB, Marx GF.Acute hydration for prevention of hypotension of spinal anesthesia in parturients. Anaesthesiology 1968; 29:374-80.
18. Bernstein CA, Waters JH, Torjman MC, Ritter D. Preoperative glycopyrrolate: oral; intramuscular, or intravenous administration. J Clin Anesth 1996; 8:515-8.
19. Ngan Kee WD, Khaw KS, Ng FF, Tam YH. Randomized comparison of closed-loop feedback computer-controlled with manual-controlled infusion of phenylephrine for maintaining arterial pressure during spinal anaesthesia for caesarean delivery. Br J Anaesth 2013; 110:59–65.
20. Ngan Kee WD. Phenylephrine infusions for maintaining blood pressure during spinal anaesthesia for cesarean delivery: finding the shoe that fits. Anesth Analg 2014;118(3):496-8.
21. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for caesarean section. Br J Anaesth 2004; 92:469–74.
22. Siddik-Sayyid S, Taha S, Kanazi G, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anaesthesia for elective cesarean delivery. Anesth Analg 2014; 118:611–8.
23. Burns SM, Cowan CM, Wilkes RG: Prevention and management of hypotension during spinal anaesthesia for elective Caesarean section: A survey of practice. Anaesth 2001; 56:794–8.
24. Langesaeter E, Rosseland LA, Stubhaug A. Continuous invasive blood pressure andcardiac output monitoring during cesarean delivery. A randomized, double-blind

comparisonof low-dose versushigh-dose spinal anaesthesia with intravenous phenylephrine or placeboinfusion. Anesthesiology 2008; 109:856–63.
25. Afolabi B B, Lesi F E, Merah NA. Regional versus general anaesthesia for caesarean section. Cochrane Database Syst Rev (2006); CD004350.
26. Solangi S A, Siddiqui S M et al. Comparison of the effects of general vs spinal anaesthesia on neonatal outcome. Anaesth Pain Intens Care 2012; 16(1):18-23.
27. Roberts S W, Leveno K J, Sidawi J E. et al. Fetal acidemia associated with regional anaesthesia for elective cesarean delivery. Obstet Gynecol 1995; 85:79–83.
28. Kinsella S M et al. international consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia 2018;73,71-92.