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Original Research Article

Comparison of Maternal and fetal effects of Ephedrine, Mephentermine and Phenylephrine for treatment of hypotension during spinal anaesthesia for Caesarean delivery

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Abstract: The objective was Ephedrine, Mephentermine, and Phenylephrine was compared in the treatment of maternal hypotension following spinal anesthesia for elective cesarean delivery. The Design was Randomized, double-blind trial and Setting in Obstetric suite at a university-affiliated hospital. The Patients were sixty healthy patients electively scheduled for cesarean delivery under spinal anesthesia. The Interventions in Patients were randomly assigned to receive either Ephedrine (n = 20) in 6 mg intravenous (IV) bolus injections, or Mephentermine (n=20) in 6 mg intravenous (IV) bolus injections, or Phenylephrine (n = 20) in 100 μg IV bolus injections to maintain systolic blood pressure (SBP) above 90 mmHg. In Results were Maternal arterial blood pressure, heart rate, Umbilical artery blood pH were measured, and neonatal Apgar scores were assessed. In the Ephedrine group, umbilical artery pH was 7.4±0.2 (mean±SD). In the Mephentermine group, umbilical artery pH was 7.3±0.1. In the Phenylephrine group, umbilical artery pH was 7.4 ± 0.1.There were significant differences between the groups in mean umbilical artery pH, although all values obtained were within normal limits. There were no significant differences between the groups in the maternal parameters or the neonatal Apgar scores. In Conclusions Mephentermine is as effective as Phenylephrine and ephedrine in the treatment of maternal hypotension, and when used in small incremental bolus injections, it appears to have no adverse neonatal effects in healthy parturients.
Keywords: Caesarean, spinal anaesthesia, systolic blood pressure (SBP)

INTRODUCTION:

Subarachnoid block is probably the most commonly administered neuraxial anesthetic for cesarean delivery because of its simplicity, speed of onset, and reliability. Because of the small doses used, there is little risk of local anesthetic toxicity and minimal transfer of drugs to the fetus. In addition; failures (including incomplete or patchy blocks) are very infrequent with spinal anaesthesia. By causing sympathectomy, spinal anesthesia augments physiological effects of pregnancy, and leads to hypotension which can have deleterious effects on mother and fetus as well. Phenylephrine and ephedrine are the most commonly used vasopressor to treat the hypotension. Mephentermine has a mixed α and β receptor agonist action with both direct and indirect effect due to release of norepinephrine and epinephrine [1]. Its impact on the heart rate is dependent on the vagal tone. Its use in hypotension after a neuraxial blockade in obstetrics is due to its ability to increase the blood pressures by augmenting the cardiac output [1].

There is scarce literature evidence on the fetal metabolic effect and placental transfer of Mephentermine [2]. However, a few studies have shown that Mephentermine is as effective as Phenylephrine in preventing maternal hypotension after spinal anesthesia and has similar effect on neonatal outcome. It is being widely used in developing countries like India as it is much more economical than Phenylephrine [3]. Therefore we designed this randomized, controlled, prospective study to compare the effect of Mephentermine as compared to the Phenylephrine and ephedrine on maternal and fetal outcomes during caesarean section under spinal anesthesia.

OBJECTIVE:

To compare the Maternal and fetal effects of Ephedrine, Mephentermine and Phenylephrine for treatment of hypotension during spinal anaesthesia for Caesarean delivery

MATERIALS AND METHODS

This study was conducted in the Department of Anaesthesiology, Jawaharlal Nehru Medical College, AMU, and Aligarh. The present research is a randomized, controlled, prospective study approved by the Departmental Board of Studies and comprised of 60 ASA I and II women aged between 20 and 40 years, with full term, uncomplicated singleton pregnancy, scheduled for elective Caesarean Section under spinal anaesthesia. A prior written informed consent was obtained from all the subjects. Prior to the procedure, detailed history, general physical examination and relevant systemic examination of all the patients were done following all standard protocols and precautions. Routine investigations such as haemogram, urine routine, renal function test, liver function tests, serum electrolytes, random blood sugar, and electrocardiogram were performed and analyzed in detail prior to procedure following all standard precautions and protocols required. Exclusion criteria consisted those who were uncooperative, unwilling, having history of anaphylaxis to local anesthetics and/or opioids and the drugs to be used, history of drug abuse, morbidly obese patients, ASA classification III, IV, V and patients having any other significant co-morbidities or any other with psychiatric disease.

Patients were randomly divided into 3 groups (M, P and E) of 20 patients each. Whenever hypotension occurred during spinal anaesthesia

Group M: received a dose of 6 mg Mephentermine, intravenously bolus.

Group P: received a dose of 100 µg Phenylephrine, intravenously bolus.

Group E: received a dose of 6 mg Ephedrine, intravenously bolus.

Hypotension was defined as a systolic pressure < 90 mmHg and during an episode of hypotension the study drug was given intravenously, as bolus. The time taken to develop hypotension and the number of boluses was noted. Symptomatic bradycardia i.e. a pulse rate of 60 /min or less with altered mental status chest pain, congestive heart failure, syncope, or other signs of shock related to the bradycardia was treated with 0.5 mg atropine intravenously [4]. Two intravenous lines were established, one line was used for infusion of fluids and the other one was reserved for infusion of Injection Oxytocine. All patients were kept nil orally for 6 hours prior to surgery. All patients were premedicated intravenously with Injection Ranitidine 50 mg IV and Injection Metoclopramide 10 mg IV. All patients were preloaded with Ringer's lactate 10 mg/kg, administered rapidly and the infusion rate was then reduced to 4 mg /kg /hr, thereafter. Hypotension, if any was managed with study drug instead of fluid. After preloading pulse rate, systolic and diastolic arterial pressures were recorded. The same parameters were recorded after spinal anaesthesia, then at every 5 minutes upto 30 min. If hypotension (systolic blood pressure<90mmHg) developed then BP was taken every 3 min till BP became normal, thereafter every 5 min. After 30 min, the blood pressure was taken every 15 min till the end of surgery. Whenever hypotension (systolic pressure less than 90mmHg) occurred the study drug was given IV bolus. The number of boluses and time taken to develop hypotension were noted. The symptomatic bradycardia i.e. a pulse rate of 60/min or less was treated with atropine 0.5mg I.V. Lumbar puncture was performed with strict aseptic precautions by a midline approach using 26 G Quincke spinal needle inserted at the L3-L4 space. After establishing a free flow of clear cerebrospinal fluid 2.5 ml of Bupivacaine (Heavy) 0.5% was injected. The patients were immediately turned supine and a wedge was placed under the right buttock for left uterine displacement. Oxygen was administered by facemask, throughout the procedure. The level of sensory loss to blunt tooth pick sensation was assessed and surgery was started when sensory loss of T6 was achieved.

Injection Oxytocine 25 IU was given after clamping the cord. Umbilical blood was sampled for acid base status. pH was assessed through blood gas analysis. Neonatal acidosis was defined as umbilical artery pH <7.20.APGAR score was taken at 1 min and 5 min .APGAR score of more than 8 at 1 min and 5 min were taken as normal , between 4-8 were moderately low while those less than 4 were taken as very low.

Table 1: APGAR score

Score	0	1	2
Respiratory effort	None	Slow/irregular	Good/crying
Heart rate/min	Absent	<100	>100
Colour of body	Blue/pale	Body pink and extremities blue	Pink
Muscle tone	Flaccid	Some flexion	Actively moving the extremities
Reflex stimulation	No response	Grimace	Cry, cough or sneezes

Newborn infants were not studied beyond the immediate post delivery period. The study continued till the end of the operation.

STATISTICAL ANALYSIS:

All observations recorded were carefully collected, segregated, categorized, tabulated, and meticulously analyzed working with a critical difference through analysis of variance and Student's t-test. Statistical calculation was done using ANOVA test to find out statistically significant result between the three groups. P<0.05 was considered significant for analysis, if the result was found to be statistically significant the Student's unpaired t-test was used to find out which group was responsible for statistically significant result.

RESULT

Table-2: Demographic profile of the subjects

Group (n=60)	Mean age (in years)	Mean weight (in Kg)	ASA Grade I (%)	ASA Grade II (%)
E(20)	25.35±3.98	52.14±3.79	68.77	31.23
M(20)	25.10±2.71	50.48±5.12	75.34	24.66
P(20)	25.40±4.23	54.10±2.23	78.67	21.33

The groups were comparable in demographic profile. Pulse rate recording were comparable in all the three groups (p>0.05) throughout the monitoring period except at 30 min when p was 0.022(i.e. <0.05), by applying Student's unpaired t test it was found that Phenylephrine and Ephedrine were better than Mephentermine in maintaining pulse rate at 30 min, and there was no statistically significant difference between Ephedrine and Phenylephrine in maintaining pulse rate at 30 min.

Table 3: Comparing the mean Pulse Rate ±SD in three groups (baseline, immediately after putting spinal anaesthesia, at 5, 10, 15, 20, 25, and 30 min).

Time(min)	Group M	Group P	Group E	p value
Baseline	89.2±14.32	89.2±10.27	84.0±9.47	0.267; p>0.05
Just after	89.2±14.32	89.2±10.27	84.0±9.47	0.267; p>0.05
5	89.3±13.66	89.5±10.40	85.0±10.67	0.949; p>0.05
10	93.1±14.65	96.3±11.11	89.9±12.72	0.300; p>0.05
15	91.0±9.72	93.4±12.75	93.0±12.64	0.791; p>0.05
20	92.8±10.27	86.9±9.0	94.7±13.6	0.078; p>0.05
25	91.0±9.92	84.9±9.50	87.3±11.15	0.173; p>0.05
30	88.4±10.89	81.6±7.32	82.1±6.27	**0.022; p<0.05**

Table 4: Demonstrating application of Student's unpaired t test to differentiate statistically significant effect of the study drug/drugs on the mean Pulse Rate±SD at 30 min

Interval	Pulse rate			Inter-group comparison		
	Group M	Group P	Group E	M-P	P-E	E-M
Pulse rate at30 min	88.4±10.89	81.6±7.33	82.1±6.27	+	_	+
				p<0.05	p>0.05	p<0.05

(+) indicates that the unpaired t-test is statistically significant**,** (-) indicates that the unpaired t-test has no statistical significance.

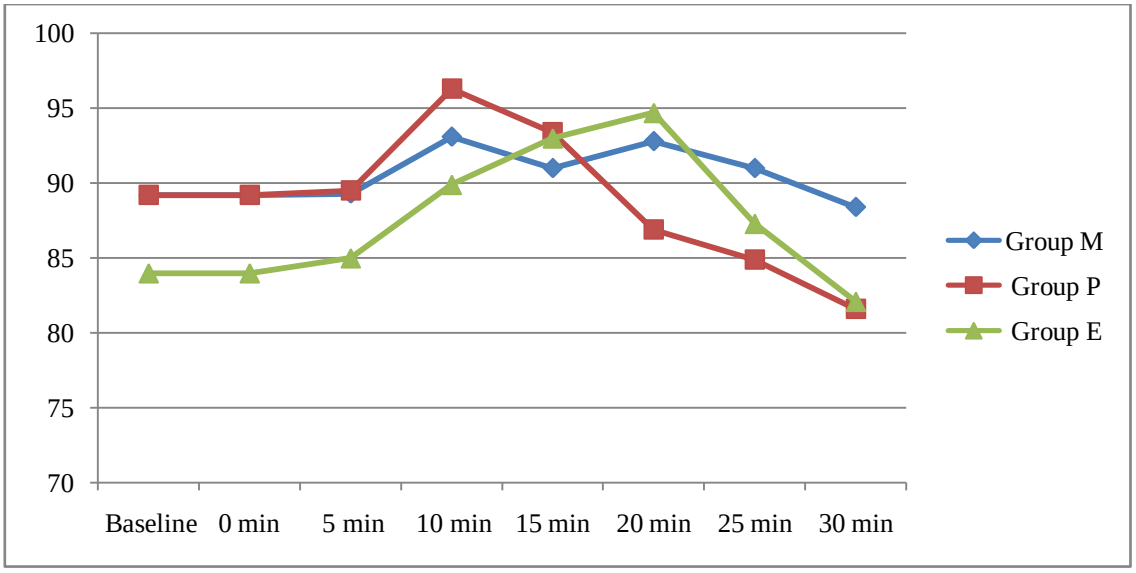

Fig 1: Illustrating the comparision of the mean pulse rate variation in the three groups

Hypotension was defined as systolic blood pressure less than 90 mm Hg, and whenever hypotension occurred the study drug was given as bolus intravenously.

Table 5: Depicting the mean Systolic Blood Pressure (mmHg) ±SD in the three groups (baseline immediately after putting spinal anaesthesia, at 5, 10, 15, 20, 25, and 30 min)

Time(min)	Group M	Group P	Group E	p value
Baseline	121.7±10.0	117.4±11.15	119.7±10.75	0.44;p>0.05
Just after	121±10.0	117.4±11.15	119.7±10.75	0.44;p>0.05
5 min	116.4±14.09	112.9±10.23	118.2±10.84	0.86;p>0.05
10 min	102.8±14.09	100.6±11.50	106.2±13.78	0.42;p>0.05
15 min	107.7±10.80	105.7±13.00	99.7±14.22	0.13;p>0.05
20 min	105.6±15.00	112.5±9.69	100.4±12.27	**0.01;p<0.05**
25 min	108.1±12.92	115.3±10.90	108.7±10.31	**0.01;p<0.05**
30 min	110.1±11.85	118.1±8.19	117.0±6.97	**0.01;p<0.05**

ANOVA test was applied to find out any statistically significant difference between the three groups in the treatment of hypotension, and it was found that upto15 min there was no significant difference between the three drugs in maintaining the systolic blood pressure but after15 min it was found that there was statistically significant difference between the groups and by application of Student's unpaired t-test it was found that Phenylephrine and Ephedrine were better than Mephentermine.

Table 6: Demonstrating application of Student's unpaired t test to differentiate statistically significant effect of the study drug/drugs on BLOOD PRESSURE at 20, 25 and 30 min

Interval	mean Systolic BP in mmHg ±SD			Intergroup comparison		
	Group M	Group P	Group E	M-P	P-E	M-E
20 min	105.6±15.0	112.5±9.7	100.4±12.3	-	+	-
25 min	108.1±12.98	115.3±10.90	108.7±10.31	-	-	-
30 min	110.1±11.8	118.1±8.2	117.0±7.0	+	-	+

(+) indicates that the unpaired t-test is statistically significant, (-) indicates that the unpaired t-test has no statistical significance.

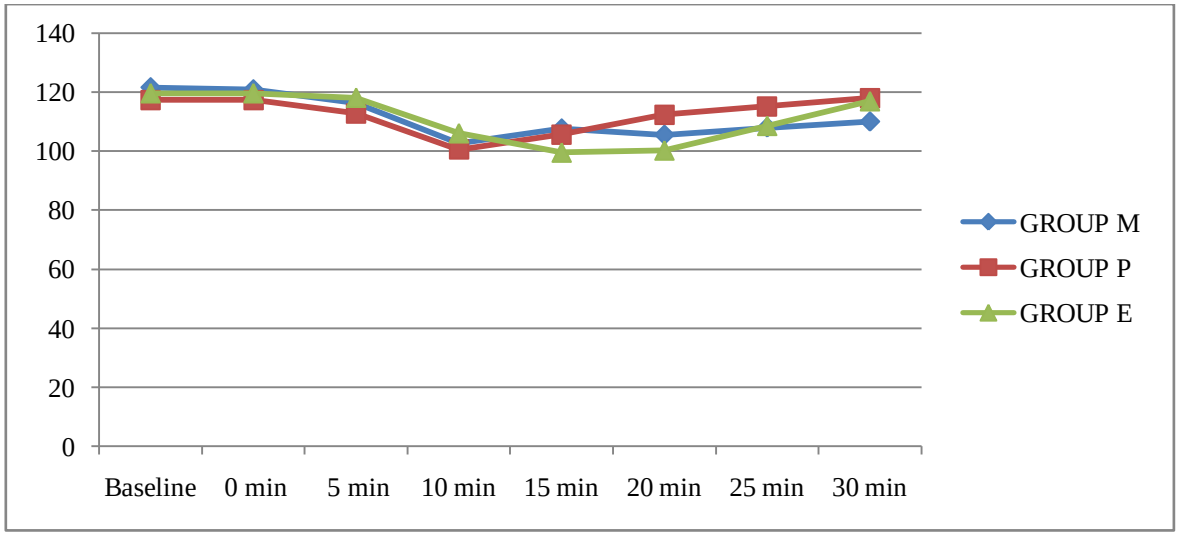

Fig 2: Showing the change in mean systolic blood (mmHg) pressure in the three groups through peri-operative period

Table 7: Illustrating the mean Diastolic Blood Pressure (mmHg) ±SD in the three groups (baseline immediately after placing spinal anaesthesia, at 5, 10, 15, 20, 25, and 30 min).

Time	Group M	Group P	Group E	p value
Baseline	79.1±7.5	75.1±7.63	75.9±5.63	0.17;p>0.05
Just after	79.1±7.5	75.1±7.63	75.9±5.63	0.17;p>0.05
5 min	76.4±6.0	75.4±7.05	75.1±5.25	0.78;p>0.05
10 min	74.2±8.0	70.0±8.33	70.8±4.92	0.16;p>0.05
15 min	75.3±7.71	73.4±9.52	69.3±5.80	0.06;p>0.05
20 min	75.1±6.66	75.0±7.21	71.2±5.56	0.10;p>0.05
25 min	77.1±7.44	76.4±5.90	74.1±4.42	0.27;p>0.05
30 min	75.7±5.12	76.8±5.37	76.7±3.80	0.73;p>0.05

There was no statistically significant difference found between the groups in maintaining the diastolic blood pressure throughout the operative period.

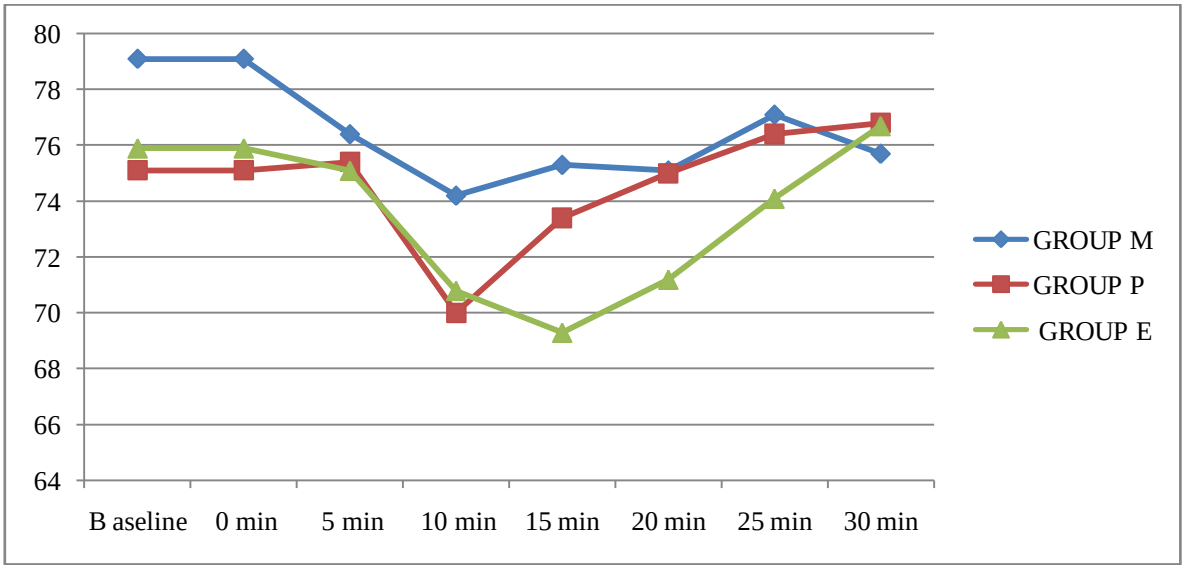

Fig 3: Displaying the variations in mean diastolic pressure in mmHg.

Table 8: Depicting the Apgar score (mean ±SD) at 1 min and at 5min after birth

APGAR score	Group M	Group P	Group E	p value
At 1 min	7.4±0.5	7.5±0.5	7.5±0.8	0.72;p>0.05
At 5 min	8.4±0.7	8.3±0.7	8.5±0.6	0.66;p>0.05

The APGAR score at 5 min was consistently higher than those at 1 min. APGAR score was normal both at 1 min and at 5 min.

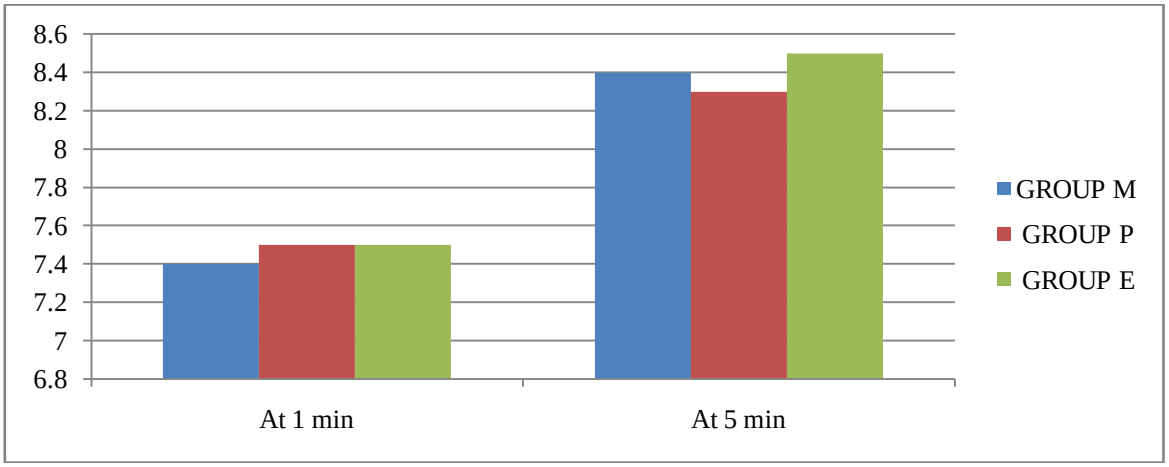

Fig 4: Depicting the mean APGAR SCORE in the three groups

Table 9: Depicting the umbilical cord pH (mean ±SD), immediately after delivery of the baby

Umbilical cord pH	Group M	Group P	Group E	p value **0.7;p>0.05**
	7.3±0.1	7.4±0.1	7.4±0.2	

There is no statistically significant difference in the umbilical cord blood pH between the three groups. Although Phenylephrine and Ephedrine have higher umbilical cord blood pH than Mephentermine, the difference is neither statistically nor clinically significant.

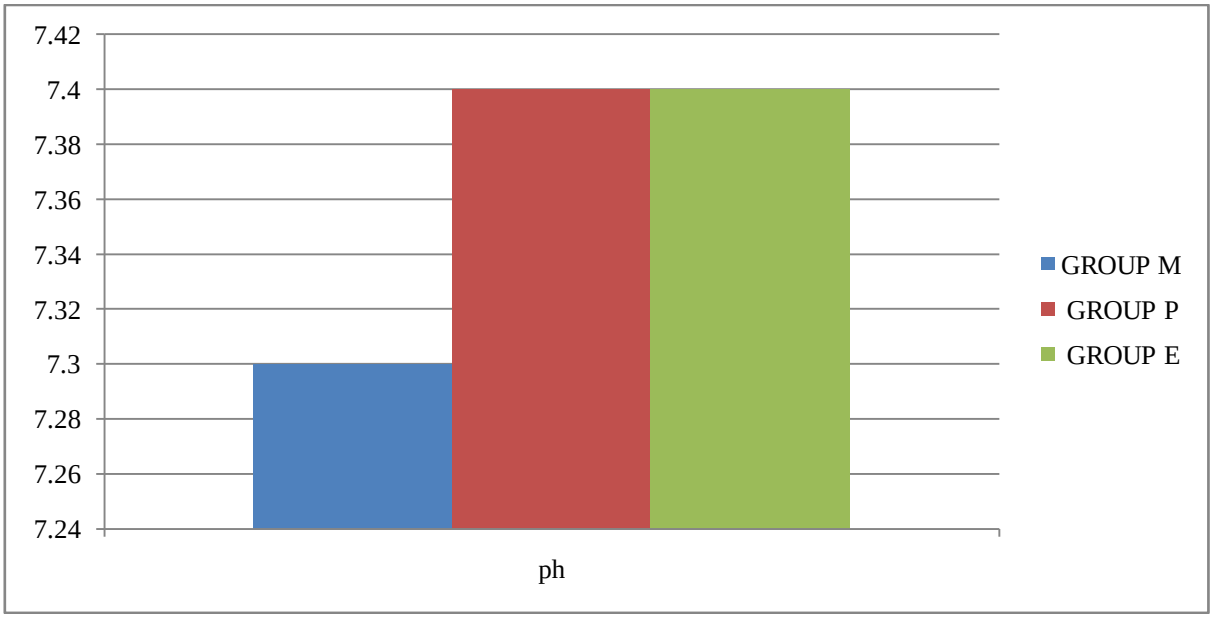

Fig 5: Showing mean umbilical cord pH immediately after the baby is out of uterus

DISCUSSION:

Sympathetic blockade after neuraxial techniques may reduce maternal blood pressure, and the decrease in pressure will affect uterine blood flow. This response may be exaggerated in patients who are not adequately prehydrated. Giving fluids intravenously (preloading) before neuraxial anaesthesia does not completely prevent maternal hypotension, but it does increase maternal cardiac output; thus, it may help to preserve uteroplacental blood flow. In previous studies the incidence of hypotension was found to be as high as 80% despite, fluid preload, lateral uterine displacement and use of vasopressor [5]. In our study the incidence of hypotension was found to be 46.6%, taking systolic blood pressure less than 90 mmHg as the definition of hypotension. The deviation from these studies is explained by differences in methodology such as volume and rate of infusion, intrathecal drug doses, vasopressor regimens, and definitions of hypotension. Hypotension occurred as early as two minutes following spinal anaesthesia. All the patients received 10 ml/Kg of Ringer's lactate as preloading prior to spinal block placement thus the intravascular volume status were assumed to be similar in all the groups. Thus the intravascular volume status did not play any significant role in the inter-group and intra-group hypotension incidences. Whenever hypotension occurred all the three study drugs were found to be effective in treating blood pressure. Up to 15 min all the three drugs were comparable in treating systolic blood pressure, but thereafter it was found that Phenylephrine was better in treating and maintaining systolic blood, also hypotension was always quicker to response to Phenylephrine. This may be due to that, Phenylephrine has peak effect within one minute, whereas Ephedrine has 2-5min and Mephentermine has 5 min [6]. All the three drugs were found to be comparable in treating and maintaining diastolic blood pressure and no statistically significant difference was found among them. These findings are in consistent with other studies [7]. At 30 min interval Phenylephrine and Ephedrine were found to be better than Mephentermine in treating/maintaining blood pressure, this observation may be explained by the fact that tachyphylaxis occurs earlier in Mephentermine. Mephentermine is a mixed sympathomimetic amine that acts indirectly (direct action through an effect on adrenergic receptor has also some contribution in its overall effects) via an action on α and β adrenergic receptors. Tachyphylaxis is explained by two different mechanisms 1) It may be due to depletion of norepinephrine stores, 2) A persistent blockade of adrenergic receptors (this mechanism explains the occurrence of tachyphylaxis in all sympathomimetics). Symptomatic bradycardia i.e. a pulse rate of 60 /min or less with altered mental status chest pain, congestive heart failure, syncope, or other signs of shock related to the bradycardia, were not found in any of the patients in any study group, although pulse rate was towards lower side in Phenylephrine group. In other studies Phenylephrine was found to cause bradycardia in about 50% of the patients [8]. This difference in the incidence of bradycardia was too, due to non-uniformity in the definition of bradycardia. In the previous studies bradycardia was defined as pulse rate less than 60/min (same as ours) but regardless of the symptoms of the low perfusion/shock that is why their studies show so high incidence of bradycardia. Phenylephrine induced bradycardia /slowing of heart rate is due to its pure α-adrenergic agonist action, which causes vasoconstriction and hence baro-receptor mediated bradycardia. Neonatal outcomes were similar in all the three groups there was no statistically significant difference between the groups. The present results confirm those reported in several previous studies on the safety of Phenylephrine in pregnancy gave an initial bolus of Ephedrine 5 mg or Phenylephrine 100µg when sensory analgesia had reached T5 [9]. This was followed by an infusion of Ephedrine 50 mg/h and Phenylephrine 1000µg/h respectively with further boluses if systolic arterial pressure decreased by 10 mm Hg from baseline. There was no change in fetal heart rate or fetal Doppler indices. Umbilical artery pH was similar in both groups. Hall *et al.;* (1994) compared a prophylactic infusion of Phenylephrine 10µg/min with Ephedrine 1 or 2 mg /min supplemented by 20µg or 6-mg boluses respectively if systolic arterial pressure decreased by 20% from baseline [10]. Although Phenylephrine (mean dose 490(range 300–680) µg) was less effective in maintaining systolic arterial pressure the umbilical artery pH was comparable in all three groups. Moran *et al.;* (1991) gave Ephedrine 5–10 mg or Phenylephrine 40–80µg when systolic arterial pressure decreased by more than 5 mm Hg from baseline values [11]. Boluses were repeated to maintain systolic arterial pressure above 100 mm Hg. Phenylephrine (total dose 335 µg) had similar vasopressor efficacy as that of Ephedrine. The umbilical artery pH was significantly higher in the Phenylephrine group. Umbilical cord pH was found to be higher in Phenylephrine and Ephedrine groups as compared to the Mephentermine group, but there was no statistically significant difference between the three groups .There was no incidence of true fetal acidosis i.e. umbilical cord pH less than 7.20. This finding was again in consistent with many previous findings [9]. Several other studies have found that Phenylephrine is better than Ephedrine in maintaining umbilical arterial pH, it is because these studies have used much larger doses of ephedrine, which is transferred through placenta and activates fetal metabolism by acting through β-adrenergic receptor, hence lower umbilical artery pH [12]. APGAR scores at 5 min were consistently found to be better than APGAR score at 1 min. APGAR scores were comparable between the three groups. This finding was in consistent with those of Sahu *et al.;*

(2003), who found that Mephentermine, Ephedrine and Phenylephrine, all are effective in maintaining neonatal APGAR scores above 7 at 5 min [13].

CONCLUSION

Following conclusions may be drawn from the present study:

1. The result of the study was not influenced by the patient age group.
2. The indications of the caesarean section did not affect the result as they were comparable.
3. The incidence of hypotension was found to be 46.6%.
4. Pulse rate recording were comparable in all the three groups ($p>0.05$) throughout the monitoring period except at 30 min when it was found that Phenylephrine and Ephedrine were better than Mephentermine in maintaining pulse rate at 30 min.
5. Upto 20 min there was no significant difference between the three drugs in maintaining the systolic blood pressure thereafter; it was found that Phenylephrine and Ephedrine were better than Mephentermine.
6. All the three study drugs were comparable in treating diastolic blood pressure.
7. Regarding the mean arterial blood pressure it was found that upto 15 min all the three drugs were comparable thereafter, Phenylephrine was always better than Ephedrine and Mephentermine, and after 30 min Ephedrine was found to be better than Mephentermine.
8. After 30 min Mephentermine was found to be less effective in treating and maintaining maternal hemodynamic parameters, as compared to Phenylephrine and Ephedrine.
9. Total no. of boluses of study drugs were comparable in all the three groups ($p>0.05$).
10. There was no incidence of symptomatic bradycardia, nausea, and vomiting.
11. Neonatal outcomes were similar in all the three groups; there was no statistically significant difference between the groups.
12. APGAR scores at 5 min were consistently found to be better than APGAR score at 1 min. APGAR scores were comparable between the three groups.
13. There was no incidence of low APGAR score either at 1 min or at 5 min.
14. Umbilical cord pH was found to be higher in Phenylephrine and ephedrine groups as compared to the Mephentermine group, but there was no statistically significant difference between the three groups.
15. There was no incidence of true fetal acidosis i.e. umbilical cord pH less than 7.20.

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