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Effect of prophylactic phenylephrine and ephedrine added to the co-loading solution on maternal hypotension, nausea and vomiting in patients undergoing caesarean section in a remote Indian Island

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ABSTRACT

Introduction and Objectives: Hypotension after spinal anaesthesia (SA) for a cesarean section may sometimes lead to significant consequences in mother and may also lead to a compromise in neonatal outcome. The objective of this study was to compare the effects of prophylactic Ephedrine and Phenylephrine to prevent hypotension, nausea, and vomiting, along with the possible changes in fetal outcome.

Materials and Methods: After approval from the institute and with informed consent, 100 parturients undergoing cesarean section under SA, and who satisfied the inclusion criteria were divided into two groups. All patients received 10 mg of 0.5% Bupivacaine heavy for SA, and the drug was injected at the L3-4 level. All parturients were co-loaded with Ringer's lactate (RL), and either 100mcg Phenylephrine or 6mg Ephedrine was added in the RL solution. Occurrences of maternal hypotension, nausea, vomiting, and APGAR score for neonate were noted and compared.

Results: Phenylephrine group had a significant reduction in the incidence of hypotension. However, it did not translate into any significant reduction in the incidence of nausea or vomiting. There were also significant differences in the APGAR scores of the neonate in 1 and 10 minutes; Phenylephrine group had a better outcome as compared to Ephedrine group.

Conclusion: Prophylactic Phenylephrine 100 mcg added to co-loading crystalloid prevents maternal hypotension significantly more than prophylactic Ephedrine 6 mg. The fetal outcome in terms of APGAR score was also better in the Phenylephrine group. However, there was no difference in the maternal heart rate, nausea, and vomiting among the groups.

1. Introduction

Spinal anaesthesia (SA) has more desirable maternal and fetal outcomes when compared to general anaesthesia and has now been accepted widely as the first choice of anaesthesia for Caesarean Section (CS).[1] However, the hypotension after the SA has remained a concern. Several techniques including the administration of intravenous fluids, vasopressors etc. are effective in preventing hypotension.[2] A study suggests that crystalloid co-loading are as effective as colloid preloading in preventing hypotension.[3] Hypotension cannot be completely prevented by co-loading or preloading alone and it has remained a common problem after SA during CS.[3] Hypotension after Spinal anaesthesia may also lead to complications like nausea, vomiting and altered consciousness in the mother, increase in the incidence of transient tachypnea of the newborn (TTN)[4,5] and reduced APGAR score in the

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newborn. Vasopressors like Mephenteramine, Ephedrine and Phenylephrine have been used for treating hypotension effectively. Many studies have been conducted, yet a recent extensive literature review indicates that the data concerning the role of Ephedrine and Phenylephrine are limited.[6] The review found that both the agents are useful for the prevention and treatment of hypotension. However, the authors concluded that further investigations are required to determine the ideal dosing regimens and overall safety.

Moreover, the concept of co-loading has been well accepted with evidence from meta-analysis at present,[7] but the effect of these two agents in conjunction with co-loading for prevention of maternal hypotension after SA is less studied. Therefore, in the present study, prophylactic Ephedrine and Phenylephrine added to the co-loading solution (Ringer's Lactate - RL) was compared for their efficacy to prevent maternal hypotension as the primary objective. The other objectives were to compare the incidence of nausea and vomiting in the mother and the effect on APGAR scores in the neonate.

2. Materials and Methods

After obtaining the approval from the institutional ethics committee, the present non-randomized study with active controls was conducted in a secondary care level hospital on an island (Andaman and Nicobar) of India. Information about the study was provided to the parturient and eligible consented parturients were enrolled for the study. The study was conducted from July 2017 to July 2018 and retrospectively registered with a Clinical Trial Registry of India (CTRI). One hundred American Society of Anesthesiologists (ASA) physical status Class II parturient with singleton fetus were enrolled for the study and allocated into two groups (i.e. Gr-P – Phenylephrine and Gr-E – Ephedrine). Alternate patients were enrolled in each group. Adult parturient in active labour of any gravida or parity were included. Parturient with comorbidities, Ecclampsia, Haemoglobin $<$ 7 gm%, Placenta previa, Placenta accreta and polyhydramnios were excluded. All patients were connected with Ringer's Lactate (RL) solution through an 18 G intravenous cannula and followed standard methods for SA in all patients. Monitoring was done as per ASA standards. 10 to 11 mg (2 – 2.2mL) of 0.5% Bupivacaine Heavy was administered in the Sub-arachnoid space in left lateral position at the level of L3-4 intervertebral space and then immediately turned to the supine position. At the time of the spinal injection, anesthesiologist's assistant was asked to add 100 mcg Phenylephrine or 6 mg Ephedrine into the RL bottle, and the fluid was administered at the rate of 15 ml/min. If the peak sensory block (to pinprick) was less than T6 after 10 minutes of spinal injection, the case was excluded. The drugs were prepared by the anesthesiologist and were not marked, and the unmarked syringe was handed over to the assistant. Patients baseline heart rate (HR), blood pressure (BP) and the Lucas urgency grade for CS were recorded. Initially, the BP, HR, and SpO2 were noted at 1, 3, 6, 10 minutes and thereafter every 5 minutes till 30 minutes. As soon as the baby was delivered, 2.5 units of Oxytocin was injected intravenously and 5 units of oxytocin per 500 mL RL was given as a slow infusion through another venous line at a rate of approximately 10 U per hour. The APGAR score was assessed and noted at 1, 5 and 10 min after delivery of the baby by the attending paediatrician, who was blinded to the patient's group. Blood loss of up to 1000 mL was taken as acceptable, and no blood was replaced. Patients who had excess bleeding and required blood transfusion were excluded. For the present study, hypotension was defined as either of systolic BP less than 90 mmHg or mean BP of less than 80% of baseline. Treatment for any noted complication was done as per the existing practice of the institute. The patient was observed for 6 hours, postoperatively for nausea and vomiting also.

The sample size for the present study was calculated based on the incidence of maternal hypotension under SA of 80%[8] without prophylaxis. We hypothesised a reduction of frequency of outcome 'maternal hypotension' of 25% with prophylaxis (i.e. expected incidence $\{80\%$ - (80% x 25%) = 60%$\}$ and expected a difference of 50% among the groups (i.e. incidences of 30% and 60%). The sample was calculated for a large population with an absolute error of 5%, power of 80% and for 95% confidence level. This gave a sample size of 50 for each group (1:1 allocation) by Fleiss method with continuity correction. (Sample size calculated using online free epidemiological tool ' OpenEpi' (www.openepi.com).

Data were entered into Microsoft Excel sheet. Further analysis of data was done using IBM SPSS statistics version 21.0. The data were presented using descriptive statistics such as frequencies, percentages, mean, standard deviation (SD) and standard error of the mean. Further, comparison of study variables was performed using an unpaired t-test, at different time intervals. The Chi-square test was used to compare the association between nausea and hypotension with drugs administered. The level of significance was set at 5%. All p-values less than 0.05 were treated as significant.

3. Results

Data from the entire 100 parturients who were enrolled in this study were eligible for analysis. The mean + SD age of the patients in Ephedrine and Phenylephrine group was similar (25.0 $\pm$ 4.29 versus 24.88 $\pm$ 3.89 years, p=0.88). The Lucas urgency grade was significantly different among the groups; Phenylephrine group was having lesser grades than Ephedrine $\{$median (q3-q1) of 3 (4-3) versus 4 (4-4) respectively, P $<$ 0.001$\}$ indicating more preoperative maternal or fetal compromised state in the Phenylephrine group.

No significant difference was noted in the HR of patients among the two groups across the entire timeline monitored (Table 1). There was no difference in the baseline systolic BP of both the groups but the systolic BP was significantly higher at 1, 3, 10, 15, 20 and 25 minutes in the Phenylephrine group (Table 2). Mean BP and diastolic BP also showed a few significantly higher readings in the Phenylephrine group as compared to Ephedrine group (Tables 3 and 4). The Phenylephrine group had less number of maternal hypotension (20% versus 68%), and the difference was highly significant, $P < 0.001$. However, no significant difference in the incidence of nausea and vomiting were noted between the Phenylephrine and Ephedrine group 4% vs 10%; p=0.24).

The baseline peripheral oxygen saturation (SpO_2) was similar {median (q3-q1) of 99 (100-98) versus 99 (100-96) in Phenylephrine and Ephedrine group respectively, P 0.06} and the SpO_2 during entire 30 minutes analysed were statistically in significant (Figure 1). The newborn weights were also similar in the groups. The median APGAR score at 1, 5 and 10 minutes were 8, 8 and 9 respectively in both the Phenylephrine and Ephedrine group. However, the neonatal outcome in terms of APGAR scores showed a significant difference at 1 and 10 minutes ($P < 0.001$) (Table 5, Figure 2).

4. Discussion

In the present study, vasopressor was added prophylactically in the co-loading solution to prevent maternal hypotension. The result of the present study indicates that 100 mcg Phenylephrine added to the 500 mL RL used for co-loading was significantly more effective in preventing maternal hypotension than 6 mg Ephedrine added to the same during first 30 minutes after SA. Maternal hypotension after SA for CS is very frequent and may have deleterious effects in mother leading to nausea, vomiting, giddiness and altered behaviour.[4] The overall incidence of maternal hypotension in the CS done under SA without any preventive measure is 80-83%.[8] Thus, it is prudent to prevent it, rather than to treat it after it occurs and leads to maternal and fetal compromise. In the present study, the incidence of maternal hypotension was only 20% in the Phenylephrine group, indicating it as an effective modality of prevention.

Use of intravenous fluid has been the most commonly practised first-line treatment of hypotension. The bolus fluid administration as preloading as well as co-loading has also been used for prevention of SA associated hypotension. A meta-analysis concluded that delaying the case for preloading even in elective surgery is unnecessary.[9] The time factor is more important in cases of emergency CS. The same meta-analysis also found that the maternal hypotension was still very high regardless of fluid loading strategy used. However, a recent meta-analysis found co-loading strategy as superior to preloading strategy for the prevention of maternal hypotension.[7] The SA induced hypotension is multifactorial; aortocaval compression and decreased systemic vascular resistance (SVR) are important factors. Studies suggest that both stroke volume and maternal cardiac output increases during the first 15 minutes after the induction of SA.[10] Literature suggests maintaining SVR, venous capacitance, and splanchnic venous tone are likely critical factors for preventing a decrease in maternal cardiac output and hypotension.[11] Therefore, it is prudent to use a multimodal approach for the prevention of maternal hypotension. In the present study, RL was used for co-loading with either of the drugs Phenylephrine 100 mcg or Ephedrine 6 mg added in the fluid. Phenylephrine is a pure alpha agonist which leads to vasoconstriction, which is likely to counter the vasodilatation due to SA related sympathectomy and a resultant decrease in BP. There may be a reflex decrease in HR due to it. Ephedrine also acts on beta receptors leading to a possible increase in HR along with a possible increase in BP. SA may sometimes lead to a decrease in HR, possibly due to a decrease in chronotropic output from under distension of atria as a result of vasodilatation. Ephedrine may counteract this bradycardia and hypotension.

As SA also reduces the HR, this effect of Ephedrine may be of potential benefit. However, in the present study, the data failed to show any difference in HR in both groups. The ages of the parturient were also not different to be a bias for HR. The present finding is, however, is contrary to the results found by Nazir et al., who found that the Phenylephrine group had significant episodes of bradycardia when compared to Ephedrine group.[12] Siddiqui et al. also found that there was a significant incidence of bradycardia in the Phenylephrine group when compared to the Ephedrine group.[13] We think there was more incidence of bradycradia since Phenylephrine was given as bolus in both these studies. Phenylephrine is quick-acting and is having a relatively shorter duration of action than Ephedrine. When given as an infusion, this may have led to a lower incidence of bradycardia in the present study. Also, for the only patient who had bradycardia in each group, we did not treat them since their BP was not low. With watchful expectation, their HR came up after few minutes.

The data from the present study indicates that there was highly significant difference ($P<0.01$) in the incidence of hypotension between the groups; the incidence of hypotension was 20% in the Phenylephrine group and 68% in the Ephedrine group. The difference was highly significant at 1, 3 and 20 minutes after the administration of SA. This may be due to the quick onset of action of Phenylephrine and some degree of tachyphylaxis to the Ephedrine at a later stage. Moslemi et al. found that there was no significant difference between the BP when they gave prophylactic Phenylephrine or Ephedrine in the infusion. This may be due to a higher dose of Ephedrine

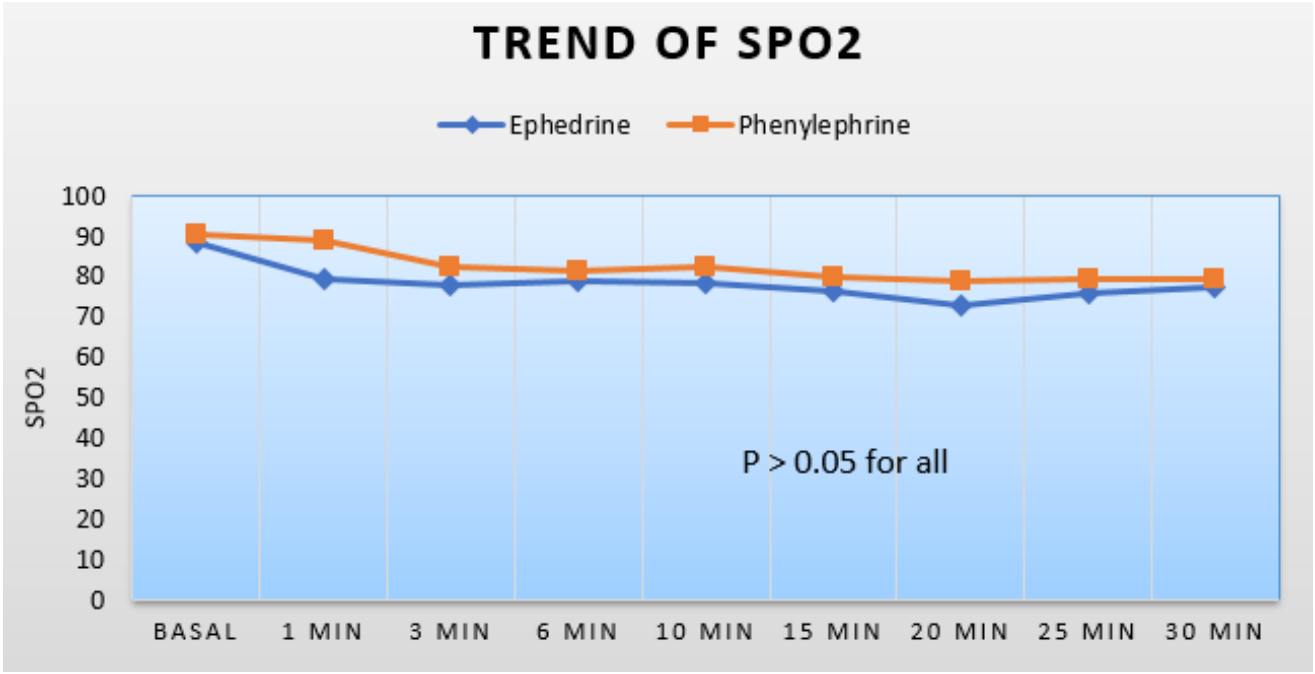

Fig. 1: Trends of mean SpO2 over the timeline

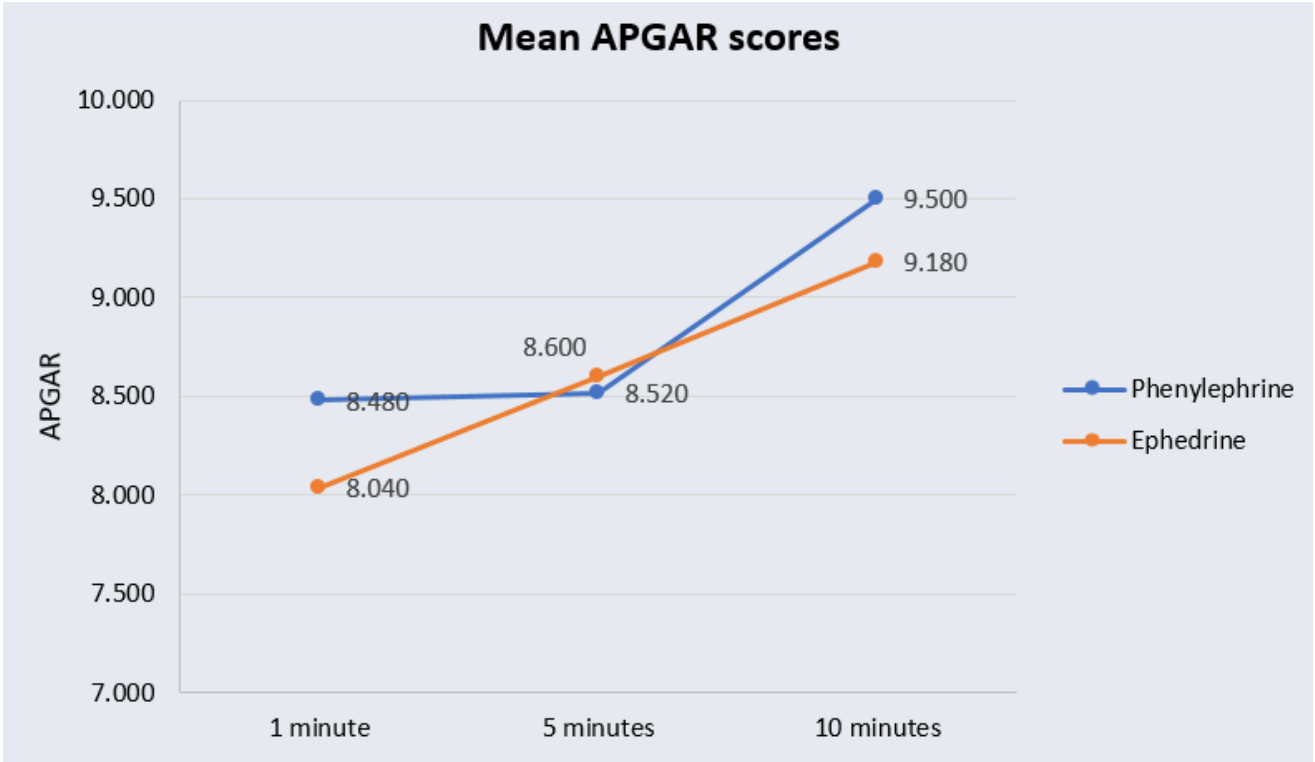

Fig. 2: Mean APGAR scores at 1, 5 and 10 minutes

Table 1: Comparison of Heart Rate across the time analysed using unpaired t-test (50 participants in each group, SD – standard deviation, SEM – standard error of the mean)

Time	Drug	Mean ± SD	SEM	t-stat	p-value
Baseline	Ephedrine	91.32 ± 20.19	2.86	0.69	0.49
	Phenylephrine	88.68 ± 17.77	2.51		
1 minute	Ephedrine	88.40 ± 18.74	2.65	0.63	0.49
	Phenylephrine	85.78 ± 19.08	2.70		
3 minutes	Ephedrine	88.92 ± 22.82	3.23	0.83	0.41
	Phenylephrine	85.32 ± 20.26	2.86		
6 minutes	Ephedrine	90.08 ± 21.69	3.07	1.18	0.24
	Phenylephrine	85.38 ± 17.93	2.54		
10 minutes	Ephedrine	87.70 ± 18.05	2.55	0.48	0.63
	Phenylephrine	86.16 ± 13.54	1.92		
15 minutes	Ephedrine	92.20 ± 17.12	2.42	1.23	0.22
	Phenylephrine	88.48 ± 12.80	1.81		
20 minutes	Ephedrine	91.70 ± 15.58	2.20	1.88	0.06
	Phenylephrine	86.72 ± 10.49	1.48		
25 minutes	Ephedrine	89.44 ± 18.35	2.60	1.28	0.20
	Phenylephrine	85.64 ± 10.05	1.42		
30 minutes	Ephedrine	90.32 ± 14.28	2.02	1.60	0.11
	Phenylephrine	86.46 ± 9.26	1.31		

Table 2: Comparison of systolic blood pressure across the time analysed using unpaired t-test (50 participants in each group, SD – standard deviation, SEM – standard error of the mean)

Time	Drug	Mean + SD	SEM	t-stat	p-value
Baseline	Ephedrine	115.30 ± 11.18	1.57	-1.96	0.053
	Phenylephrine	120.10 ± 13.35	1.89		
1 minute	Ephedrine	105.76±13.89	1.96	-4.33	0.001
	Phenylephrine	117.90 ± 14.12	2.00		
3 minutes	Ephedrine	103.88 ± 12.52	1.77	-2.70	0.01
	Phenylephrine	110.63±12.52	1.77		
6 minutes	Ephedrine	105.72 ± 12.31	1.74	-1.46	0.15
	Phenylephrine	109.12±10.86	1.54		
10 minutes	Ephedrine	104.90 ± 12.71	1.80	-2.20	0.03
	Phenylephrine	110.14±11.04	1.56		
15 minutes	Ephedrine	103.04 ± 12.73	1.80	-2.00	0.05
	Phenylephrine	107.48 ± 9.26	1.31		
20 minutes	Ephedrine	100.30 ± 10.89	1.54	-3.06	0.001
	Phenylephrine	106.54 ± 9.43	1.33		
25 minutes	Ephedrine	102.26±11.60	1.64	-2.15	0.03
	Phenylephrine	106.68 ± 8.78	1.24		
30 minutes	Ephedrine	104.02±8.78	1.24	-1.45	0.15
	Phenylephrine	106.42 ± 7.71	1.09		

used in that study (45 mg in 250 ml infusion).[14] However, Mercier et al. found that there was significantly more incidence of hypotension in the group given prophylactic Ephedrine even when given at high doses. They observed that the incidence of hypotension reduced significantly if the prophylactic infusion also contained Ephedrine.[15]

Alkassi et al. found that there were more incidences of nausea and vomiting in the Ephedrine group than in the Phenylephrine group.[16] We found that there was no difference in the incidence of nausea and vomiting from the time of SA until 6 hours between the Phenylephrine and Ephedrine group. Again, this may be due to the lower dose of Ephedrine used in our study. Also, the higher incidence of hypotension did not lead to a higher incidence of nausea and vomiting, probably due to the lesser severity of hypotension and prompt correction of it. Moreover, the effect of the drug, especially Phenylephine added to the co-loading fluid is expected to be over soon after the completion of administration, while nausea and vomiting were assessed for 6 hours. Furthermore, the baseline risk of nausea vomiting may not be similar in the two groups we studied, and it was not possible to compare and match as it

Table 3: Comparison of diastolic blood pressure across the time analysed using unpaired t-test (50 participants in each group, SD – standard deviation, SEM – standard error of the mean)

Time	Drug	Mean + SD	SEM	t-stat	p-value
Baseline	Ephedrine	74.90±10.80	1.53	-0.09	0.93
	Phenylephrine	75.10 ± 11.77	1.66		
1 minute	Ephedrine	66.34±11.63	1.64	-3.74	0.001
	Phenylephrine	74.56±10.29	1.46		
3 minutes	Ephedrine	64.62 ± 12.41	1.76	-1.46	0.15
	Phenylephrine	68.11 ± 11.46	1.62		
6 minutes	Ephedrine	64.92 ± 10.71	1.52	-1.33	0.19
	Phenylephrine	67.56±9.08	1.28		
10 minutes	Ephedrine	64.74±11.15	1.58	-1.81	0.07
	Phenylephrine	68.42±9.06	1.28		
15 minutes	Ephedrine	62.54 ± 12.44	1.76	-1.26	0.21
	Phenylephrine	65.72±12.72	1.80		
20 minutes	Ephedrine	58.88 ± 14.90	2.11	-2.39	0.02
	Phenylephrine	64.82 ± 9.36	1.32		
25 minutes	Ephedrine	62.12±10.52	1.49	-1.59	0.12
	Phenylephrine	65.20 ± 8.81	1.24		
30 minutes	Ephedrine	63.70±9.95	1.41	-1.21	0.23
	Phenylephrine	65.86 ± 7.82	1.10		

Table 4: Comparison of mean blood pressure across the time analysed using unpaired t-test (50 participants in each group, SD – standard deviation, SEM – standard error of the mean)

Time	Drug	Mean	SEM	t-stat	p-value
Baseline	Ephedrine	88.37 ± 10.48	1.48	-.80	0.43
	Phenylephrine	90.10± 11.22	1.59		
1 minute	Ephedrine	79.48± 11.71	1.66	-4.25	0.001
	Phenylephrine	89.01 ± 10.65	1.51		
3 minutes	Ephedrine	77.71 ± 11.88	1.68	-2.04	0.04
	Phenylephrine	82.29 ± 10.49	1.48		
6 minutes	Ephedrine	78.52± 10.64	1.50	-1.51	0.13
	Phenylephrine	81.41± 8.37	1.18		
10 minutes	Ephedrine	78.13 ± 11.16	1.58	-2.06	0.04
	Phenylephrine	82.33 ± 9.11	1.29		
15 minutes	Ephedrine	76.04± 12.13	1.72	-1.61	0.11
	Phenylephrine	79.64 ± 10.10	1.43		
20 minutes	Ephedrine	72.69 ± 12.56	1.78	-2.81	0.001
	Phenylephrine	78.73 ± 8.53	1.21		
25 minutes	Ephedrine	75.50± 10.51	1.49	-1.88	0.06
	Phenylephrine	79.03 ± 8.07	1.14		
30 minutes	Ephedrine	77.14± 8.94	1.26	-1.39	0.17
	Phenylephrine	79.38± 7.10	1.00		

Table 5: Comparison of APGAR and baby weight (50 in each group, SD – standard deviation, q3-q1 – interquartile, $median (q3-q1), #mean + SD).

Parameter	Drug	Mean + SD Or Median (q3 – q1)	t-stat	P value
APGAR At birth$	Ephedrine	8 (8-8)	-4.82	< 0.001
	Phenylephrine	8 (9-8)		
APGAR 5 minutes$	Ephedrine	8 (9-8)	0.74	0.46
	Phenylephrine	8 (9-8)		
APGAR 10 minutes$	Ephedrine	9 (9-9)	-3.55	< 0.001
	Phenylephrine	9 (10-9)		
Birth weight#	Ephedrine	2.80 + 0.35	-1.31	0.191
	Phenylephrine	2.89 + 0.30		

was not within our primary objectives.

Although umbilical blood pH has been taken as one of the markers of fetal distress in the literature, APGAR score now has been established as a comparable indicator of holistic wellbeing of the newborn, not inferior to the umbilical pH study. Josten et al. concluded that even when technically feasible, routine cord pH measurements add little to the evaluation of neonatal well-being and its management.[17] In our study, although we had planned to collect this data, due to logistic and technical issues, data from only a few cases were available, and we have not analysed those in the final stage. However, there was significantly ($P < 0.01$) better APGAR scores in the Phenylephrine group than in the Ephedrine group in the present study. This is against the finding of Nazir et al., who observed that there was no significant difference in the APGAR scores between the group containing Phenylephrine and the group between Ephedrine.[12]

The present study has some limitations. The study was non-randomized. Although we planned umbilical blood pH assessment, due to technical issues, only a few pH data could be assessed, and therefore we had to exclude that parameter from the analysis. The present study parturient was without any comorbidities and straight forward uncomplicated, non-high risk patients. So, the results of the present study may not be extrapolatable for high-risk parturient or parturient with comorbidities. We only analysed the maternal hypotension for 30 minutes after the induction of SA. Although all babies were delivered and expected to be delivered by CS within this time, maternal hypotension after SA can still occur after 30 minutes and affect the condition of the mother. Our study cannot comment on whether the nausea vomiting until 6 hours would have been different among the groups with maternal hypotension if the maternal hypotension would have been monitored beyond 30 minutes. Therefore, future studies with high-risk parturient, the randomised design involving multicentre will give a better idea. There is emerging evidence of norepinephrine in the management of maternal hypotension, and Ephedrine may not be used in many parts of the world. Although we have taken emergency CS, the numbers of Lucas grade 1 patients were very minimal, and, so the extrapolation of this study result can be limited to Lucas grade 2-4 CS only.

There were few things which were relatively new in this study. The incidence of Phenylephrine induced bradycardia which is often dreaded, was not significant, probably due to it was given as an infusion and when present it needed not to be corrected due to BP being maintained. Ephedrine group had significant episodes of hypotension later during the surgery probably due to the tachyphylaxis of its usage. Also, there can be socio-demographic changes to the response of drugs and this study is the first of its kind in this Island.

5. Conclusion

With the present data, we conclude that along with RL, co-loading with added prophylactic Phenylephrine 100 mcg prevents maternal hypotension significantly more than prophylactic Ephedrine 6 mg. The fetal outcome in terms of APGAR score was better at 1 and 10 minutes in an uncomplicated parturient with Phenylephrine than Ephedrine. However, there was no difference in the maternal heart rate, nausea, and vomiting.

6. Acknowledgement

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7. Contribution details

NR – concept, design, data collection, clinical work, literature search, manuscript preparation; HMRK - concept, design, data analysis, interpretation, literature search, manuscript editing and review; AN - concept, design, data collection, clinical work, revision; MD - concept, design, data collection, clinical work; AP- concept, design, data collection, clinical work, RS - concept, design, data collection, clinical work. EPS – Clinical work, data collection, calculations.

8. Financial support

None

9. Conflicts of interest

None.

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