Original Research Article

Comparison of IV bolus phenylephrine, ephedrine and mephentermine for maintenance of hemodynamic status and its effect on fetal outcome during spinal anesthesia in cesarean section

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Abstract

Background: Maternal hypotension during spinal anesthesia for cesarean section is a persistent problem which can result in adverse maternal and fetal outcome.

Aim: Aim of this study was to compare the efficacy of IV bolus phenylephrine, ephedrine and mephentermine for the maintenance of hemodynamic status and its effect on fetal outcome during spinal anesthesia in cesarean section**.**

Materials and Methods: We did prospective randomized double blind study in 60 patients. They were undergoing elective cesarean section under spinal anesthesia and who developed hypotension after subarachnoid block. The patients were randomly divided into three groups of 20 each. Phenylephrine Group (Group P) received Inj. Phenylephrine 100 mcg IV, Group E received Inj. Ephedrine 6 mg IV and Group M received Inj. Mephentermine 6 mg IV bolus. Whenever hypotension occurred, patients received the study drug. After administration of drugs and their consistence

maintenance till end of 60 minutes. Patients were compared with respect to age, weight, duration of surgery, Systolic BP, Diastolic BP, Mean Arterial Pressure and Heart Rate.

Results: The rise of systolic, diastolic and mean arterial pressure in Group P was significantly high for first 4min of bolus dose as compared to Group E & Group M ($P<0.05$). APGAR scores were ≥7 in all the three groups.

Conclusion: It was concluded that IV bolus Mephentermine is as effective as Phenylephrine and Ephedrine in maintenance of arterial blood pressure during spinal anesthesia in cesarean section with good neonatal outcome.

Key words

Anesthesia, Cesarean section, Spinal Anesthesia, Hypotension, Arterial Blood Pressure, Phenylephrine, Ephedrine, Mephentermine.

Introduction

Spinal anesthesia is an effective and safe method of regional anesthesia. In spite of numerous advantages, it has few complications. The most common hemodynamic complication is hypotension [1] with its incidence upto 50% to 80% in obstetrics population [2]. Prolonged maternal hypotension is detrimental to the fetus. Many prophylactic and rescue measures have been recommended for the prevention and treatment of hemodynamic instability, like preloading or co-loading with crystalloids or colloid, avoidance of aorto-caval compression and use of vasoactive agents. Vasopressors are the cornerstone in treatment of hypotension during spinal anesthesia. We studied IV bolus Phenylephrine, Ephedrine and Mephentermine for maintenance of hemodynamic status during spinal anesthesia in caesarean section.

Hypothesis

During spinal anesthesia in Caesarean section. Intravenous bolus Mephentermine is as effective as Phenylephrine and Ephedrine in the maintenance of hemodynamic status with no adverse effects on fetal outcome.

Materials and methods

After obtaining the ethical approval from the Institution Review Board and the Department of Anesthesiology, Institute of Medicine, a prospective randomized double blind study was conducted on 60 patients at Tribhuvan University Teaching Hospital, Nepal for a period of 4 months. Informed consent was taken from each patient. ASA Gr I and Gr II patients with baseline Systolic BP between 100-140 mm Hg and Diastolic BP between 70-89 mm Hg scheduled for elective caesarean section who developed hypotension during intra-op periods were included in the study.Whereas patients with medical diseases like diabetes, RHD, severe anemia, and cerebrovascular diseases, patients with obstetrical complications like antepartum hemorrhage, pregnancy induced hypertension, cord complications (nuchal cord or cord prolapse), fetal malformations, polyhydramnios, and multiple pregnancies and any contraindication to spinal anesthesia were excluded from the study.

Patients were randomized into 3 groups of 20 each using sealed envelope technique.

Group P – received Phenylephrine 100 microgram (1 ml) as iv bolus

Group E – received Ephedrine 6 mg (1 ml) as iv bolus

Group M – received Mephentermine 6 mg (1 ml) as iv bolus

Drug was prepared by Anesthetic Assistant or Anesthesia Resident who were not involved in the study.

All patients underwent pre-anesthetic evaluation, kept nil per oral for 6 hours and received oral premedication with Ranitidine 150 mg and

Metoclopramide 10 mg the night before and the early morning of surgery. In preparation room Ringer's Lactate (10 ml/Kg) was infused intravenouly and baseline vital parameters like Heart rate, Systolic BP and Diastolic BP were recorded. Patients were then shifted to OT. ECG, BP, SpO2 were attached and monitored.

Under all aseptic precautions and in sitting position, SAB was performed with 25 G Quincke's Spinal needle. 2.2 ml of 0.5% Bupivacaine (Heavy) was injected intrathecally in 15-20 seconds at L_{3-4}/L_{2-3} intervertebral space. The patient was then placed supine with left lateral tilt. Sensory level (block height) achieved was assessed in every 5 minutes and sensory level achieved at 15 minutes were recorded for the study. The level of Motor blockade was assessed every 5 minutes and till 15 minutes according to Bromage Scale.

Surgery was started after achieving sensory block level of T4/T6. Whenever Hypotension occurred, patient received the study drug as IV bolus which is considered as 0 min. For purpose of this study, Hypotension was defined as fall in systolic pressure >20% from the baseline value or a value less than 90 mmHg [3]. Pulse rate, Systolic BP, Diastolic BP and Mean arterial pressures were recorded at every 2 minutes till 20 minutes and thereafter every 5 minutes till 60 minutes. If hypotension doesn't get corrected by giving 3 bolus doses of study drug then rescue drugs Inj Adrenaline 10 mcg was given and repeated as necessary. IV Atropine 0.6mg was given for heart rate less than 50 bpm.

After delivery of baby, cord was clamped, 5 units oxytocin was given as iv bolus followed by 10 units of injection oxytocin in Ringer's lactate as slow iv infusion. Pediatrician assessed APGAR scores at 1 and 5 minutes after delivery and were noted. Total amount of IV fluid given (maintenance and bolus), amount of vasopressor and atropine required during intraoperative period was recorded. Any untoward effects like nausea / vomiting, shivering, restlessness during intra-operative period was noted and treated.

Statistical Analysis

All the data was analyzed using Statistical Package for the Social Sciences (SPSS) 17. Comparability of groups were analysed using ANOVA, Chi Square, Independent t and Paired t test. P value < 0.05 was considered significant.

Results

Demographic Comparison: All the 3 groups; Group E, Group P and Group M were comparable with respect to age of patients, weight of patients and duration of surgery. There was no statistical significant difference in age distribution of patients (p = 0.922), weight distribution of patients (p = 0.965) and duration of surgery (p = 0.2) as per **Table - 1**.

Table – 1: Patients Characteristics and Relevant Data.

	Group E – Ephedrine	**Group M – Mephentermine**	**Group P - Phenylephrine**	**P value**
Maternal age (Mean ± SD) yrs	27.25 ± 4.711	26.70 ± 4.846	26.75 ± 4.756	0.922
Maternal weight (Mean ± SD) kgs	62.55 ± 11.83	61.70 ± 8.99	62.18 ± 9.81	0.965
Duration of Surgery (Mean ± SD) mins	43.5 ± 11.3	34.15 ± 10.3	37.01 ± 9.7	0.2

Characteristics of Subarachnoid Block:- At 15 minutes, all patients in 3 groups achieved sensory level at T4 and motor block of Grade 4 Bromage scale.

Comparison of Hemodynamic Parameters:-

Trend of Mean SBP, Mean DBP and Mean Arterial Pressure: After administration of study drugs, there was rise in mean Systolic blood pressure and mean diastolic blood pressure at all the time intervals and were within normal range and were comparable among all three groups. In

intergroup comparison: No significant differences ($p > 0.05$) were observed in mean systolic blood pressure and mean diastolic blood pressure between Group E and Group M at any of the time intervals (Table 2, 3 and 4 respectively). But, at 4 min interval post use of study drugs, rise in mean SBP and mean DBP compared between Group P and Group E were statistically significant ($p <$ or $= 0.001$). Similarly, at 4 min interval, the rise in mean SBP and mean DBP in Group P were more compared to Group M and it were statistically significant ($p < 0.001$) as per **Table – 2, 3, 4**.

Table - 2: Changes in Mean Systolic Blood Pressure (mm Hg) (Mean ± SD).

Interval (in mins)	Group E	Group M	Group P	E vs M (p value)	E vs P (p value)	M vs P (p value)
Baseline	119.70 ± 9.59	121.70 ± 11.27	120.25 ± 11.41	0.549	0.467	0.222
0	87.50 ± 7.86	83.85 ± 12.80	84.85± 11.00	0.284	0.386	0.792
2	107.40 ± 12.51	105.40 ± 17.23	108.75 ± 17.76	0.677	0.783	0.549
4	110.55 ± 14.22	107.15 ± 13.88	125.00 ± 9.44	0.449	0.001	<0.001
6	112.50 ± 14.11	113.85 ± 10.41	115.65± 13.75	0.733	0.677	0.412
8	112.55 ± 9.18	115.45 ± 10.07	119.80± 17.33	0.347	0.534	0.215
10	115.85 ± 13.99	115.60 ± 13.47	120.85± 10.38	0.954	0.446	0.474
12	118.90 ± 9.54	115.75 ± 13.09	121.85 ±12.62	0.390	0.150	0.155
14	112.65 ± 14.18	115.70 ± 11.14	118.85± 10.20	0.454	0.959	0.404
16	116.15 ± 12.91	112.85± 11.27	120.25± 12.28	0.395	0.471	0.915
18	117.45 ± 11.63	109.25± 18.01	119.90± 14.75	0.095	0.547	0.285
20	116.65 ± 7.38	113.75± 14.04	121.45 ± 9.83	0.419	0.428	0.856
25	118.80 ± 7.36	114.25± 11.67	120.00± 12.18	0.149	0.076	0.742
30	115.90 ± 8.78	115.40± 10.46	118.50± 10.12	0.871	0.894	0.976
35	115.70 ± 8.90	113.90± 9.35	116.20 ± 9.77	0.537	0.867	0.670
40	114.87 ± 8.51	114.85± 9.38	114.91 ± 9.14	0.995	0.990	0.987
45	116.00 ± 8.43	113.33± 14.04	119.11 ± 9.94	0.618	0.369	0.834
50	115.78 ± 8.06	114.22± 10.32	120.13 ± 4.76	0.726	0.430	0.787
55	115.29 ± 8.50	114.67± 12.08	117.86 ± 5.67	0.910	0.518	0.531
60	118.00 ± 8.37	121.29 ± 3.86	117.83 ± 3.49	0.378	0.965	0.121

Trend of HR: Heart rate raised in all three study groups at 0 mins interval i.e. when hypotension occurred. But, after the administration of study drug, there was a significant drop in HR at 4 mins interval in Group P as compared to both Group M and Group E .($p < 0.001$). At rest of intervals, it was statistically non-significant and within normal limits ($p > 0.05$) as per **Table – 5**.

Number of patients received Drug Bolus after onset of Hypotension: In Group E, 45% (9) patients required single bolus dose while 30% (6) required two bolus and 25% (5) required three bolus doses to maintain systolic blood pressure within normal range. In Group M, 45% (9) required single, 35% (7) two bolus and 20% (4) three bolus doses. Whereas, in Group P 45% (9) required single, 30% (6) required two and 25% (3) required three bolus doses. Statistically not significant ($p > 0.05$) (**Figure - 1**).

In Group E 1 patient received injection Adrenaline bolus thrice and in Group M, 1 patient received Injection Adrenaline bolus once along with fluid bolus.

Side Effects: 2 patients developed Bradycardia in Group P, after drug bolus at 4 mins and 6 mins. It was not seen in any other group. 20% (4) patients in Group E and 15% (3) in Group M developed intraoperative nausea during hypotension. In Group P, 5% (1) patient developed shivering. No statistical significant difference.

Table - 3: Changes in Mean Diastolic Blood Pressure (mm Hg) (Mean ± SD).

Interval (in mins)	Group E	Group M	Group P	E vs M (p value)	E vs P (p value)	M vs P (p value)
Baseline	76.35 ± 9.10	76.35 ± 09.10	74.65 ± 10.99	0.592	0.597	0.597
0	55.70 ± 9.74	55.70 ± 09.74	50.85 ± 10.14	0.519	0.131	0.131
2	64.85 ± 12.65	64.85 ± 12.65	70.80 ± 13.77	0.825	0.163	0.163
4	67.40 ± 10.99	67.40 ± 10.99	82.25 ±5.95	0.899	<0.001	<0.001
6	69.85 ± 11.65	69.85 ± 11.65	71.05 ± 10.95	0.180	0.739	0.739
8	71.10 ± 9.99	71.10 ± 09.99	75.45 ± 13.16	0.702	0.216	0.216
10	70.45 ± 11.52	70.45 ± 11.52	69.15 ± 09.02	0.688	0.693	0.693
12	74.20 ± 8.10	74.20 ± 08.10	76.05 ± 10.61	0.183	0.298	0.298
14	69.20 ± 12.11	69.20 ± 12.11	70.90 ± 09.34	0.703	0.622	0.622
16	69.50 ± 11.92	69.50 ± 11.92	71.00 ± 09.68	0.738	0.665	0.665
18	69.15 ± 11.49	69.15 ± 11.49	70.25 ± 09.52	0.957	0.744	0.744
20	71.90 ± 9.41	71.90 ± 09.41	70.50 ± 08.26	0.144	0.620	0.620
25	72.85 ± 9.86	72.85 ± 09.86	75.50 ± 09.33	0.243	0.160	0.160
30	76.00 ± 6.81	76.00 ± 06.81	78.50 ± 09.45	0.076	0.017	0.017
35	76.50 ± 7.01	76.50 ± 07.01	79.50 ± 08.13	0.125	0.044	0.044
40	75.20 ± 9.25	75.20 ± 09.25	76.73 ± 04.67	0.023	0.425	0.425
45	73.00 ± 6.75	73.00 ± 06.75	75.11 ± 07.82	0.340	0.579	0.579
50	71.11 ± 6.01	71.11 ± 06.01	73.38 ± 07.76	0.137	0.611	0.611
55	71.43 ± 6.90	71.43 ± 06.90	70.00 ± 06.45	0.158	0.696	0.696
60	68.00 ± 4.47	68.00 ± 04.47	71.67 ± 07.53	0.694	0.365	0.365

APGAR Scores: All three groups had good neonatal outcome. All neonates in all three groups had APGAR scores ≥7 (**Table – 6**).

Discussion

Preloading with I.V. crystalloid or colloid solution is a standard practice for prevention of hypotension after spinal anaesthesia, but, this practice has been found to be ineffective when used alone, without concomitant use of vasopressor drugs. Sympathetic blockage resulting in vasodilatation is the primary cause of fall in arterial blood pressure, so use of vasopressor agents in conjugation with fluid preloading appears to be more logical approach to correct it. Inadequately treated hypotension occurring during caesarean section can cause undue effects on both mother and fetus.

Ephedrine and mephentermine, both are mixed sympathomimetic amines that act both directly and indirectly on α and β adrenergic receptors, whereas phenylephrine is a pure α agonist which stimulates α1-adrenergic receptors by a direct effect. There have been several attempts to find the optimal therapy for spinal anaesthesia induced hypotension during C section.

Thomas DG and colleagues [4], in their similar randomized trial study of bolus phenylephrine (100 mcg) versus ephedrine (5mg), reported that both drugs are equally effective in restoring

cardiac output and maternal systolic blood pressures above 100 mm Hg.

Kansal A, et al. [5] found that mephentermine can be used as safely and effectively as ephedrine for the management of hypotension during spinal anaesthesia in patients undergoing elective Caesarean section. Neonatal APGAR scores acid base profiles were also comparable in both groups.

Table - 4: Changes in Mean Arterial Pressure (mm Hg) (Mean ± SD).

Interval (in mins)	Group E	Group M	Group P	E vs M (p value)	E vs P (p value)	M vs P (p value)
Baseline	86.60± 11.01	90.50 ± 09.37	88.15 ± 07.74	0.235	0.610	0.393
0	65.40 ± 09.10	64.00 ± 10.79	67.75 ± 09.81	0.660	0.381	0.704
2	75.50± 13.38	75.75 ± 13.49	80.20 ± 14.95	0.953	0.301	0.329
4	77.25± 12.93	77.90 ± 11.49	96.45 ±05.92	0.867	**<0.001**	**<0.001**
6	80.50 ± 14.16	81.05 ± 09.89	81.05 ± 10.55	0.887	0.890	1.000
8	84.95 ± 11.99	86.05 ± 10.91	88.00 ± 13.98	0.218	0.392	0.092
10	85.80 ± 08.81	86.05 ± 10.31	88.40 ± 09.40	0.758	0.085	0.202
12	80.70 ± 11.68	83.65 ± 09.31	83.30 ± 10.45	0.458	0.440	0.306
14	81.70 ± 12.04	83.95 ± 09.53	84.70 ± 09.23	0.341	0.772	0.828
16	82.75 ± 10.95	80.25 ± 09.45	85.95 ± 09.43	0.674	0.954	0.417
18	81.60 ± 11.66	82.35 ± 09.07	83.20 ± 10.62	0.901	0.843	0.849
20	82.20 ± 13.38	81.35 ± 10.80	85.60 ± 06.69	0.944	0.648	0.766
25	83.00 ± 09.75	81.00 ± 10.41	84.65 ± 07.92	0.753	0.646	0.892
30	84.50 ± 08.24	82.90 ± 09.71	86.05 ± 08.65	0.974	0.192	0.670
35	85.20 ± 07.76	82.00 ± 07.55	88.18 ± 08.20	0.323	0.432	0.705
40	84.60 ± 07.26	83.07 ± 07.96	84.56 ± 03.57	0.463	0.989	0.965
45	84.56 ± 07.18	79.56 ± 12.65	85.88 ± 07.02	0.295	0.836	0.315
50	86.43 ± 04.35	79.44 ± 06.23	88.29 ± 06.03	0.126	0.584	0.158
55	84.60 ± 03.91	80.67 ± 09.62	87.00 ± 09.09	0.165	0.417	0.457
60	82.25 ± 08.08	85.86 ± 07.15	87.20 ± 05.18	0.731	0.403	0.752

Bhardwajand colleagues [6] compared phenylepherine, metaraminol and ephedrine and found all the three vasopressors were equally effective in maintaining maternal blood pressure as well as umbilical pH without any detrimental effects on fetal and maternal outcome.

Recent studies by Simin, et al. [7], Muñoz E, et al. [8]and Nazir, et al. [9] also concluded ephedrine and phenylephrine are both effective vasopressores for treatment of hypotension (no significant difference) associated to spinal block during caesarean section without adverse effects on infants/neonates.

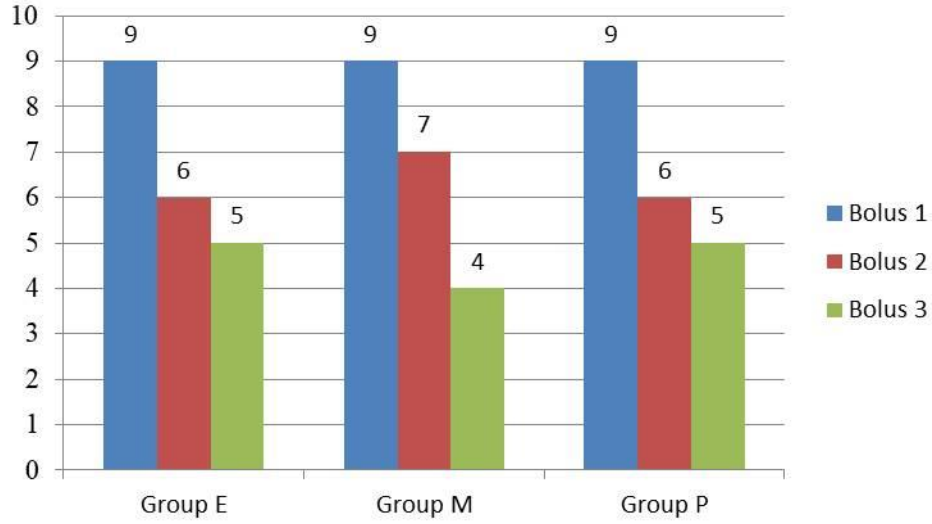
Ramanathan, et al. [10] and Adigun TA [11], reported that bolus ephedrine (5 mg) is equipotent to iv bolus phenylephrine (100 mcg) for the maintenance of maternal arterial blood pressure.

In a similar comparative study of bolus phenylephrine 100 mcg and mephentermine 6 mg study, R. Sharma, et al. [12] showed that there was rise in mean SBP and DBP was significantly higher in phenylephrine group ($p < 0.05$), at all the time intervals compared to mephentermine group.

Table - 5: Changes in Heart Rate (bpm) (Mean ± SD).

Interval (in mins)	Group E	Group M	Group P	E vs M (p value)	E vs P (p value)	M vs P (p value)
Baseline	92.20± 11.97	91.10 ± 10.44	92.15 ± 09.38	0.758	0.988	0.740
0	98.60± 18.12	103.80± 15.12	105.00 ±12.03	0.331	0.196	0.783
2	87.35± 07.61	82.70± 12.80	83.55 ± 07.24	0.171	0.162	0.344
4	88.90± 11.09	87.45± 08.99	74.05 ± 08.36	0.652	0.000	0.000
6	84.40± 09.20	87.15± 09.85	80.70 ± 05.04	0.367	0.257	0.034
8	85.10± 07.35	85.55± 05.72	82.65 ± 04.32	0.830	0.207	0.078
10	85.45± 08.00	85.95± 08.95	83.00 ± 05.74	0.853	0.273	0.222
12	85.10± 08.44	87.00± 07.21	83.15 ± 04.66	0.449	0.371	0.052
14	86.10± 08.05	87.25± 07.93	82.10 ± 04.62	0.652	0.633	0.301
16	85.85± 07.10	85.75± 08.63	80.70 ± 03.23	0.968	0.932	0.981
18	87.80± 08.11	86.10± 08.93	79.65 ± 04.15	0.532	0.298	0.839
20	87.25± 07.37	87.70± 08.83	82.25 ± 04.87	0.862	0.137	0.134
25	88.60± 07.06	88.05± 09.17	85.85 ± 04.75	0.833	0.157	0.347
30	86.60± 08.38	89.60± 05.83	80.25 ± 03.92	0.197	0.866	0.140
35	87.95± 07.10	87.35± 06.95	82.45 ± 05.10	0.789	0.082	0.141
40	88.79± 07.28	87.40± 06.86	81.53 ± 03.89	0.575	0.262	0.657
45	88.69± 07.86	88.67± 08.11	84.82 ± 04.07	0.994	0.962	0.957
50	89.00± 04.90	88.89± 08.98	85.53 ± 03.00	0.973	0.390	0.629
55	93.43± 06.27	89.00± 09.47	86.00 ± 03.27	0.305	0.170	0.439
60	93.14± 09.69	89.71± 04.82	85.50 ± 02.07	0.418	0.086	0.073

Figure - 5: Number of Patients Received Drug Bolus.



In our study, all the three vasopressors effectively maintained mean blood pressure and mean arterial pressure within normal range of baseline value though phenylephrine maintained better mean blood pressure and arterial pressure in first 4 minutes of bolus dose ($p<0.05$) as compared to ephedrine and mephentermine. This may be attributed to the fact that phenylephrine has a peak effect within one minute, whereas ephedrine at 2-5 minutes and mephentermine at 5

minutes. These results are in good correlation with similar studies conducted by Devender D, et al. [13], Anil kumar G, et al. [14], Bhattarai B, et al. [3] and Sahu D, et al. [15], where the rise in mean systolic and diastolic blood pressure were found to be statistically more significant ($p < 0.001$) in phenylephrine group till 6 mins of bolus dose as compared with ephedrine and mephentermine groups. Consistent results were found in the study conducted by Lakshmi Mahajan, et al. [16] where maternal blood pressure was higher in group P, compared with group E and M which was statistically significant ($p<0.001$) at different time intervals till 14th minute.

Table - 6: APGAR scores [Median (minimum, maximum)].

	1 min	**5 min**
Group E	7 (7,8)	8 (8,9)
Group M	8 (7,8)	8 (8,9)
Group P	7 (7,8)	8 (8,8)

In this study, heart rate significantly dropped after bolus dose of phenylephrine at 4 mins ($p < 0.001$) as compared to mephentermine and ephedrine. The incidence of bradycardia in the phenylephrine group may be explained due to its lack of action on beta receptors. Consistent results are obtained in phenylephrine treated women in other studies [3, 4, 8, 10, 13-17] also.

This study showed APGAR scores of baby at 1 min (≥ 7) and 5 min(≥ 8) with good neonatal outcome in all three groups. Similar results were obtained in the studies conducted by M Mohta, et al. [17] and others [3, 4, 8, 10-16] also.

Conclusion

We have found that iv bolus mephentermine is as effective as phenylephrine and ephedrine in maintenance of arterial pressure during spinal anaesthesia, though phenylephrine has quicker peak effect in comparison to other two drugs and it causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable. APGAR scores in all 3 groups were high and comparable at 1 min and 5 min.

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