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A Comparative Study between Ephedrine and Mephentermine in Management of Hypotension Following Spinal Anaesthesia for Caesarean Section

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Abstract
Aim: *To conduct a comparative study between Ephedrine and Mephentermine in Management of Hypotension following Spinal Anaesthesia for Caesarean Section (ASA Gr I & II with Bupivacaine (heavy).*
Methodology: *The present study of comparison between Mephentermine and Ephedrine to treat Spinal Hypotension in Caesarean Section was undertaken after approval of the hospital ethical committee and written informed consent of parturients undergoing caesarean section with ASA Grade I and Grade II, they were included in this study. One hundred such parturients who had developed hypotension following spinal anaesthesia were randomly assigned to two groups of 50 each as per study drug.*
Results: *The peak action of Ephedrine in increasing Systolic BP was attained in a mean time of 3.66 minutes whereas it took a longer mean time of 4.04 minutes in the Mephentermine Group. Further, the increased Systolic BP was maintained over a mean time 9.24 minutes in Ephedrine Group as compared to a lesser time of 7.98 minutes in Mephentermine. Similarly, the Diastolic BP was also well maintained in Ephedrine Group as compared to Mephentermine Group. Bradycardia and hypotension (due to SAB on account of blockade of cardioacceleratory fibers) was more effectively treated with Ephedrine than Mephentermine. Ephedrine also caused tachycardia in more number of parturients. The requirement of top up bolus dose was more in Mephentermine Group than in Ephedrine Group. Injection Atropine was required in 10% of parturients in Mephentermine Group whereas this was not necessitated in the Ephedrine Group. Side effects like nausea vomiting and headache were reported to a lesser extent in Ephedrine Group as compared to Mephentermine Group.*
Conclusion: *On the basis of the above findings it may be concluded that Ephedrine is more potent than Mephentermine in management of hypotension following spinal anaesthesia for caesarean section. As such, Ephedrine is the vasopressor of choice in obstetrics.*

I. Introduction

The type of anaesthesia for caesarean section depends on the indications for the operation, degree of urgency, desires of the patients and the judgment of the anesthesiologist. Caesarean section may be done under general anaesthesia or regional anaesthesia; each of the technique having its own merits and demerits. General anaesthesia for caesarean section has of late become obsolete due to various reasons such as risk of failed intubation, aspiration of gastric contents and the requirement of additional depressant agents. On the other hand, regional anaesthesia has gained popularity in the recent past due to absence or minimal biochemical and metabolic changes. The ability of the mother to remain awake and enjoy the birthing experience and reduced blood loss under regional anaesthesia are some of the factors which outweigh the benefits of general anaesthesia for caesarean delivery. Epidural or Spinal anaesthesia can be used for caesarean section. [1] Spinal anaesthesia was introduced into clinical practice by August Bier in 1898 even before the break-through of orotracheal intubation by Franz Kuhn in 1901. Spinal anaesthesia has many advantages over epidural anaesthesia. For instance, spinal anaesthesia can be performed with one single shot, which has been found to provide faster, dense and superior blockade, allowing the surgical incision to be made sooner resulting in shorter total operating room time. The rapid onset of anaesthesia with subarachnoid anesthetics makes spinal anaesthesia an ideal choice to be used in emergency caesarean sections. Spinal anaesthesia not only produces a more profound blockade than epidural anaesthesia, the need for supplementary intravenous analgesics and anxiolytics is also decreased. [2] Because the dose of local anesthetics used with spinal anaesthesia is small, there is little chance of maternal toxicity and very minimal placental transfer of drug to fetus. Hyperbaric Bupivacaine is the most commonly used agent for spinal anaesthesia when performing caesarean section. [3]The duration of action lasting from one and half to two hours is perfectly matched to the duration of surgery in most cases. It is generally used in doses that depend on patient's height and amount of the drug.[4] The technique of spinal anaesthesia, however, allows a definite duration of anaesthesia and witnesses higher incidence of

maternal hypotension. The unavoidable sequence of spinal anaesthesia is blockade of sympathetic preganglionic efferents leading to peripheral venous pooling causing hypotension. Therapies are primarily aimed at reducing the severity of hypotension; they include prophylactic leg elevation and wrapping, use of inflatable boots, preloading of the patient with crystalloids and colloids, lateral uterine displacement in obstetric patients, and vasopressors used as last resort with varying results.[5] The present study was undertaken to compare Ephedrine and Mephentermine in Management of hypotension following spinal anaesthesia with Bupivacaine (heavy) for Caesarean Section.

II. Materials And Methods

The present study of comparison between Mephentermine and Ephedrine to treat Spinal Hypotension in Caesarean Section was undertaken at the Government Maternity Hospital, Nayapul, Sultan Bazar Maternity Hospital, and Nilofur Hospital, Hyderabad during the period October 2007 to December 2009. After approval of the hospital ethical committee and written informed consent of parturients undergoing caesarean section with ASA Grade I and Grade II, they were included in this study. Patients with cardiovascular or respiratory disorders, hypertension, preeclampsia, diabetes and those on medication which have direct cardiac effects such as beta blockers were not included in this study. One hundred such parturients who had developed hypotension following spinal anaesthesia were randomly assigned to two groups of 50 each as per study drug. The routine investigations like haemoglobin, bleeding & clotting time, random blood sugar, serum creatinine, blood urea, ECG and urine for protein and sugar was carried out in all parturients. All patients were befasted overnight and did not receive any pre-operative medication. Group I was administered 6 mg of Ephedrine and Group II with 6 mg of Mephentermine at the onset of spinal hypotension.

After bringing the parturient in the Operation Theatre, all baseline monitors for recording NIBP, pulse rate, SPO2 and ECG were attached to them. Thereafter they were administered preloading of 10 to 15 ml / kg ringer lactate after securing wide bore IV cannula (18 G) before the procedure. For assessing the baseline hemodynamic values in each parturient, three recordings of Non-Invasive arterial Blood Pressure (NIBP), pulse rate, SPO2 was made before subarachnoid block. Lumbar puncture was made in the left lateral position under full aseptic precautions at L3- L4 inter space. Once free flow of cerebro spinal fluid (CSF) was obtained, 2.0 ml of hyperbaric bupivacaine was injected intrathecally. All patients were turned supine with wedge under the right hip for left uterine displacement and supplemental oxygen 5 litre per minute was given through facemask. Level of pinprick sensation was assessed and surgery started when sensory level of T6 achieved. Hypotension was defined as decrease of systolic BP by more than 30% of the baseline pressure or less than 90 mm/hg whichever is higher. Hemodynamic changes were recorded at the time of onset of hypotension. If the supplemental IV fluid failed to reverse hypotension, a bolus IV dose of ephedrine or mephentermine was administered and the drug was repeated if necessary. Thereafter NIBP, HR and SPO2 were recorded at every two minutes till the 10^{th} minute, then at 15^{th}, 20^{th} and 30^{th} minute interval for the purpose of the present study. After delivery of the baby, injection oxytocin 15 units in 500 ml of RL was given after clamping of the umbilical cord or if necessary, injection methergin 0.2 mg IM was given. The apgar score of the baby was observed and blood loss assessed and observed for residual hypotension post-delivery of placenta. Any side effects of the study drug such as nausea, vomiting, tachycardia, headache, etc., were observed and recorded. The surgery was generally completed within 30 minutes in each case.

III. Observations and Results

Table 1 shows division of parturients into study drug groups, age distribution of parturients in the two groups, weight distribution, and height distribution.

Age in years	**Group I (ephedrine)**	**Group II (mephentermine)**	**P Value**
19-22	26	28	>0.05
23-26	19	14	
27-30	5	8	
Mean age ±S.D.	22.72 ± 2.63	23.18 ± 3.14	
Weight in KGs			**P Value**
50-55	10	16	>0.05
56-60	32	23	
61-65	7	10	
66-70	1	1	
Mean weight ±S.D.	58.16 ± 3.25	57.98 ± 4.10	
Height in CMs			**p. Value**
146-150	8	14	
151-155	25	21	
156-160	14	12	
161-170	3	3	

Mean height ±S.D.	154.02 ± 4.02	153.30 ± 4.80	>0.05

Table 2 shows mean Systolic BP of parturients in the two groups over different time intervals, mean Diastolic BP of parturients in the two groups over different time intervals.

Intervals	**Group I (ephedrine)**	**Group II (mephentermine)**	**P Value**
	SBP in mm hg (Mean ± S.D.)	SBP in mm hg (Mean ± S.D.)	
Baseline	121.70 ± 7.70	123.80 ± 7.24	>0.05
HP (VP Given)	81.60 ± 6.30	81.88 ± 6.03	>0.05
2 min after VP	110.96 ± 10.07	108.74 ± 5.94	>0.05
4 min after VP	119.44 ± 9.39	114.84 ± 9.62	<0.05
6 min after VP	118.66 ± 9.32	112.88 ± 7.41	<0.01
8 min after VP	115.36 ± 6.96	104.72 ± 6.34	<0.001
10 min after VP	110.44 ± 7.19	97.06 ± 7.58	<0.001
15 min after VP	108.90 ± 7.32	97.42 ± 6.14	<0.001
20 min after VP	108.98 ± 7.02	98.16 ± 5.34	<0.001
30 min after VP	110.78 ± 5.95	101.04 ± 4.82	<0.001
Intervals	**Group I (ephedrine)**	**Group II (mephentermine)**	**P Value**
	DBP in mm hg (Mean ± S.D.)	DBP in mm hg (Mean ± S.D.)	
Baseline	79.66 ± 5.00	79.72 ± 4.89	>0.05
HP (VP Given)	44.28 ± 6.10	44.12 ± 5.75	>0.05
2 min after VP	70.06 ± 8.04	67.02 ± 4.85	<0.05
4 min after VP	74.22 ± 5.70	71.84 ± 4.97	<0.05
6 min after VP	73.78 ± 6.92	70.48 ± 4.71	<0.01
8 min after VP	71.44 ± 5.65	65.46 ± 5.07	<0.001
10 min after VP	68.42 ± 5.33	62.06 ± 4.74	<0.001
15 min after VP	67.56 ± 5.10	62.14 ± 4.81	<0.001
20 min after VP	68.14 ± 4.45	64.04 ± 4.64	<0.001
30 min after VP	69.02 ± 4.34	68.68 ± 4.36	>0.05

SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, VP-Vasopressor, HP-Hypotension.

Table 3 shows mean arterial pressure of parturients in the two groups over different time intervals, mean heart rate of parturients in the two groups over different time intervals.

Intervals	**Group I (ephedrine)**	**Group II (mephentermine)**	
	MAP in mm hg	MAP in mm hg	
Baseline	94	94	
HP (VP Given)	57	57	
2 min after VP	84	81	
4 min after VP	89	86	
6 min after VP	89	85	
8 min after VP	86	79	
10 min after VP	82	74	
15 min after VP	81	74	
20 min after VP	82	75	
30 min after VP	83	79	
Intervals	**Group I (ephedrine)**	**Group II (mephentermine)**	**p. Value**
	H.R. per min. (Mean ± S.D.)	H.R. per min. (Mean ± S.D.)	
Baseline	81.82 ± 6.46	86.72 ± 8.47	>0.05
HP (VP Given)	82.86 ± 8.08	82.30 ± 12.07	>0.05
2 min after VP	101.40 ± 7.50	92.40 ± 7.26	<0.001
4 min after VP	108.52 ± 8.11	94.74 ± 8.41	<0.001
6 min after VP	107.72 ± 9.08	92.08 ± 8.05	<0.001
8 min after VP	104.90 ± 8.38	89.54 ± 7.86	<0.001
10 min after VP	101.28 ± 7.41	87.36 ± 8.58	<0.001
15 min after VP	100.88 ± 6.34	88.22 ± 7.92	<0.001
20 min after VP	99.60 ± 5.21	89.38 ± 7.63	<0.001
30 min after VP	98.06 ± 4.52	88.74 ± 6.97	<0.001

MAP-Mean Arterial Pressure, HR-Heart rate, HP-Hypotension, VP-Vasopressor.

Table 4 shows - (A) Time taken for BP to reach peak level in the parturients in two groups. (B) Time till which increased BP sustained in the parturients in two groups.

Time taken to reach peak level	**Group I (Ephedrine)**	**Group II (Mephentermine)**	**P Value**
Mean time ±S.D	3.66 ± 1.36	4.04 ± 1.11	>0.05
Maintenance of increased BP			
Mean time ±S.D	9.24 ±1.39	7.98 ± 2.36	<0.01

IV. Discussion

Many studies have been reported which compared between ephedrine and mephentermine in management of hypotension following spinal anaesthesia for caesarean section. The ease and long history of success has made Subarachnoid Block the anaesthetic procedure of choice for surgeries involving the lower abdomen / lower limbs particularly in obstetrics. Though spinal anaesthesia has a wide range of advantages like the simplicity of technique, its rapid onset of action, economical and minimal postoperative complications, it is not without the risk of physiological side effects on the various systems. The most common side effects of spinal anaesthesia are hypotension and bradycardia. Hypotension is due to the combined effects of sympathetic blockade and the added effect of vagal nerve predominance which leads to peripheral venous pooling causing decrease in preload, arteriolar vasodilatation causing decrease in afterload and blockade of cardio-accelerator fibers (T1-T4) leading to bradycardia and decrease in contractility further reducing the blood pressure. Dr. Hemant Bhagat, Dr. Kiran Malhotra, Dr Sudhir K Ghildyal, ed al stated that maternal hypotension is also responsible for fetal bradycardia and acidosis[6]**.** Spinal anaesthesia induced hypotension is treated physiologically by improving the venous return so as to increase the preload thereby restoring the cardiac output. R. Sharma, N. Mitra & M. Niyogi have stated that Cesarean section under spinal anaesthesia is commonly associated with hypotension which can be detrimental to mother and fetus. It is the responsibility of the anesthesiologists to ensure stable arterial blood pressure throughout surgery to avoid any decrease in maternal organ blood flow and placental insufficiency.[7] Hypotension is the most common side effect of regional anaesthesia, which if not treated properly can cause severe vomiting,

loss of consciousness, aspiration and cardiac arrest in the mother. The baby may suffer from hypoxia, acidosis and hypoxic brain injury. There are various strategies to prevent hypotension following regional anaesthesia namely lateral uterine displacement, mechanical leg compression, intravenous fluid pre-load and vasopressors**.** The most effective strategy is the use of the appropriate vasopressors with intravenous fluid. In this regard the primary aim should be to maintain the maternal BP at baseline value without sparing the use of appropriate vasopressors and intravenous fluids. Regional Collins had stated in his *Principles of Anaesthesiology* that Ephedrine is probably the first choice for prophylaxis and treatment of spinal anaesthesia hypotension; Mephentermine is also effective and is a second choice.[8] With this backdrop, the present comparative study between Mephentermine and Ephedrine in management of hypotension following spinal anaesthesia for Caesarean Section (ASA Gr I & II with Bupivacaine (heavy) was undertaken and the results are discussed under separate subheadings as follows. One hundred Parturients who had developed hypotension following spinal anaesthesia for Caesarean Section were allocated randomly into two groups of 50 each. As their systolic blood pressure had fallen below 82 mmHg (i.e. about 30% of the baseline value) within 3 to 5 minutes following SAB they received bolus dose of Ephedrine (Group I) and Mephentermine (Group II) after crystalloid preloading of 10-15 ml/kg and avoidance of aortocaval compression. All the parturients were constantly monitored clinically in the intra operative period and none of them had changes in respiratory rate or oxygen saturation.

Physical Characteristics of Parturients in two Groups: The mean age, weight and height of parturients in Group I (Ephedrine) was 22.72±2.63 years, 58.16±3,25 kgs and 154.10±3.67 cms respectively whereas in the Group II (Mephentermine) the same were recorded at 23.18±3.14, 57.98±4.10 and 153.30±4.80 respectively. The p.value on all these three parameters at <0.05 was statistically not significant and the inter group differences should not affect the outcome of the study. However, in two patients in Group I, more than one bolus dose of the study drug Ephedrine given was given to accelerate BP whereas in Group II, Mephentermine was required to be given twice to five patients to improve their Systolic Blood Pressure. The sensory block in these patients had reached up to T4 stage and after the SAB, their Systolic BP had either not increased considerably or had dropped below the tolerable limits after initial increase during the perioperative period.

Hemodynamic changes: (i) Systolic Blood Pressure (SBP): Kansal et al, in August 2004 compared the efficacy of IV infusion in a different dosage regimen i.e. ephedrine 2.5mg.min-1 and mephentermine 2.5mg.min-1 after an initial bolus of 5mg in each group, for the treatment of hypotension and concluded 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.[9] In the present study, following the intrathecal block, the baseline mean SBP in Group I declined by 33% from 121.70 to 81.60 mmHg and in Group

II it declined by similar margins of 34% from 123.80 to 81.88 mmHg in the first 3 to 5 minutes. The p.Value of >0.05 at these two stages were statistically insignificant. With the injection of the bolus study drugs the SBP in both Groups increased steadily. Sahu ed. el. compared ephedrine 6mg and mephentermine 6mg IV bolus doses and concluded that the initial response for increase in SBP was better with use of ephedrine than with mephentermine**.** [10] The findings of the present study correlates with this result. SBP in Group I (Ephedrine) increased to 110.96 mmHg in the 2nd minute whereas in Group II it rose to 108.74 mmHg. The p.Value >0.05 was statistically not significant. However, in the 4th minute the mean SBP reached to a peak value of 119.44 mmHg (46% increase over Hypotensive (HP)value)) in Group I which was more pronounced than Group II wherein it had increased to a peak of 114.84 mmHg(40% increase over HP value). This difference with a p.Value of <0.05 was statistically significant. The SBP started decreasing gradually from 6th minute onwards but the decline was sharper in Group II (Mephentermine) than in the Group I. At the 30th minute the mean SBP of Group I was 110.78 mmHg and that of Group II was 101.04mmHg. Though the SBP was maintained well above the initial hypotensive stage in both the Groups till the end of the study time i.e. up to 30th minute, the difference in SBP of the Group I was significantly higher than that of Group II from the 8th to 30th minute with p.Value of <.001 throughout this period. Further, in two parturients in Group I (4%) the top up dose of study drug Ephedrine was required to be given whereas top up doses were required to be given in five parturients (10%) in Mephentermine Group as the initial dose of the study drug was not enough to accelerate the SBP beyond acceptable level. It was observed that with the top up dose of ephedrine, patients developed tachyphylaxis. The second important aspect captured in the hemodynamic changes was the time taken in the two Groups for the NIBP to reach their peak levels after administration of the study drug and the time over which this increase was sustained before it started plummeting. Dr.Dinesh Sahu, Dr.Dilip Kothari and Dr.Amrita Mehrotra in 2003 concluded in their clinical study on comparison of bolus ephedrine, mephentermine and phenylephrine that ephedrine has a peak effect within 2-5 minutes and mephentermine has an average of 5 minutes.[10] The findings of the present study correlate with this result. In Group I (Ephedrine), it took a mean time of 3.66 ± 1.36 minutes for the BP to reach its peak, whereas in Group II the peak BP was achieved in a bit longer time of 4.04±1.11 minutes. The p.Value of >0.05 is statistically insignificant. The increased BP was, however, maintained for a mean time of 9.24±1.39 minutes before declining sharply in Group I and in Group II the improved BP was sustained for a comparatively shorter duration of 7.98±2.36 minutes. The p.Value of <0.01 has high statistical significance.

(ii) Diastolic Blood Pressure (DBP): The mean DBP in Group I had declined from the base line value of 79.66 to 44.28 mmHg after SAB and from 79.72 to 44.12 mmHg in Group II. This difference with p.Value >0.05 was statistically not significant. However from the 2nd minute onwards after administration of study drug, DBP increased steadily in both the Groups and reached a peak of 74.44 mmHg (68% increase over HP stage) in Group I (Ephedrine) and touched 71.84 mmHg (63% increase over HP stage) in Group II at the 4th minute. The increase in DBP was evidently sharper in Group I as compared to Group II up to the 20th minute of the study with high statistical significance (p.Value <0.001). At the 30th minute the difference narrowed down and the mean DBP reached 69.02 mmHg in Group I and 68.68 mmHg in Group II. The p.Value of >0.05 was statistically not significant.

(**iii) Mean Arterial Pressure (MAP):** The MAP derived in both the Groups at baseline and HP stage was 94 mmHg and 57 mmHg respectively. The same displayed an increasing trend after administering the study drugs and increased by 59 % (to 89mmHg) in Group I (Ephedrine) and to a lesser extent of 51% (to 86 mmHg) in the Group II at the 4th to 6th minute interval. The MAP declined thereafter in both the Groups but the rate of decline was sharper in Group II when it reached 79 mmHg at the 30th minute as compared to 83 mmHg in Group I. As MAP is a derived value, statistical analysis on this parameter was not conducted. However, the trend of difference in MAP in both the Groups implies to a comparatively superior placental circulation and perfusion to major organs of the body in Group I (Ephedrine) than in the Group II (Mephentermine). This aspect is also reflected in a better Apgar score recorded in Group I.

(iv) Heart Rate: Lakshmi Mahajan, L K Anand & KK Gombar, in their double blind comparative study on ephedrine, mephentermine and phenylephrine found that no episodes of bradycardia was noted in ephedrine and mephentermine groups. [11] The findings of the present study correlates with this result. The mean Heart Rate (HR) of parturients in Group I (Ephedrine) increased slightly from baseline of 81.82 beats per minute (BPM) to 82.86 at the time of SAB whereas the same declined from 86.72 to 82.30 BPM in Group II. The p.Value was >0.05 and not significant. After giving the study drugs, HR improved at a rapid pace and reached a peak of 108.52 BPM (31% increase) in Group I while it increased at a considerably rate and attained a peak value of 94.74 BPM (15% increase) in the Group II at the 4th minute interval. The p.Value of <0.001 indicated very high statistical significance. The mean HR thereafter started gradual deceleration in both the Groups but was maintained at a much higher level in the Group I than in Group II throughout the study period. The difference was highly significant statistically with p.Value <0.001. At the 30th minute the mean HR in Group I was 98.06 BPM while the same in Group II was 88.74(p. value <0.001). During the perioperative period,

injection Atropine 0.5 mg was administered to five parturients to treat bradycardia due to SAB in Group II as the bolus dose of Mephentermine was unable to accelerate their HR where as in Group I there was no such instance. This aspect signifies a greater effectiveness of Ephedrine in treating bradycardia caused by SAB when compared to Mephentermine.

Side Effects: In the Group I (Ephedrine), eight parturients had developed palpitations due to increased cardiac activity (HR), two had headache and one parturient reported nausea and another reported nausea with vomiting. The side effects like nausea, vomiting and headache were thus reported only in four parturients (8%) in Group I. Robert K Stoelting stated that the substitution of a hydroxyl group on the beta carbon of the ethylamine side chain (ephedrine) decreases CNS stimulant effects due to decreased lipid solubility.[12] This is presumably the reason for low incidence of side effects in ephedrine group. On the other hand, side effects were reported in more number of parturients (15 parturients i.e. 30%) in the Group II with four patients complaining of nausea, three having headache, three has nausea with vomiting, four with nausea plus headache and one had nausea together with vomiting and headache. Major causes of nausea and vomiting has been ascribed in part to a reduction in medullary blood flow to the chemoreceptor trigger zone. An increase in gastric peristalsis due to preganglionic sympathetic denervation of the stomach may also provoke nausea and vomiting during spinal anaesthesia. The lesser instance of these side effects may, therefore, be on account of increased mean arterial pressure and presumably improved medullary blood flow in the Group I (Ephedrine) when compared to the Group II. There was no incidence of drug induced bradycardia and hypertension in both the groups.

APGAR: The APGAR score did not reveal any untoward effect on foetal status since all the new born babies of the two Groups had APGAR score of more than 7 which was considered good.

Blood Loss: The mean blood loss of parturients in Group I and Group II was in the similar range of 345 ml and 347 ml respectively. The difference was not significant. (p.value >0.05).

V. Conclusion

On the basis of the above findings it may be concluded that Ephedrine is more potent than Mephentermine in management of hypotension following spinal anaesthesia for caesarean section. As such, Ephedrine is the vasopressor of choice in obstetrics.

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