Original Research Article

Comparison of prophylactic infusion of phenylephrine and norepinephrine for prevention of hypotension in elective caesarean section under spinal anaesthesia- A randomized controlled study

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Abstract

Background: Post spinal hypotension can have deleterious effects on parturient and foetus in caesarean section if not prevented. Norepinephrine has alpha agonistic activity with weak beta agonistic activity, so may be more effective in maintaining cardiac output of parturient. **Aims:**To compare the effects of prophylactic infusion of phenylephrine and norepinephrine on cardiac output as a primary outcomeand heart rate, mean arterial pressure, stroke volume, and systemic vascular resistance of parturient, neonatal Apgarscore and umbilical blood gas analysis as secondary outcomes.**Method**:Eighty six healthy patients undergoing elective caesarean section under spinal anaesthesia were randomized into two groups. Group P received infusion of phenylephrine (100 µg/ml)intravenous (iv) and Group N received infusion of norepinephrine (5µg /ml) iv just after intrathecal drug administration.The pre-defined algorithm was used to adjust the infusion rate according to mean arterial pressure. All haemodynamic parameters and total volumes of vasopressor upto the time of uterine incision and upto 30 min after starting drug infusion were recorded. Data were compared using unpaired Student t-test and Chi square test. P value less than 0.05 was considered significant. **Results**: Group N had higher cardiac output at 1 min (p=0.01),3 min(p=0.0001),6 min(p=0.006), 9 min(p=0.001) in comparison to group P. Group P had lower heart rate at 1 min (p=0.0003),3 min(p=0.0001),6 min(p=0.0001), 9 min(p=0.0001) and 12 min(p=0.0078) in comparison to group N. Systemic vascular resistance was higher in group P at 6 min(p=0.004),9 min(p=0.001) and 12 min (p=0.04). Total volume of vasopressor required to maintain mean arterial pressure was higher in group N(p<0.0001). **Conclusion:** Norepinephrine has greater efficacy to maintain cardiac output, with greater heart rate in comparison to phenylephrineduring spinal anaesthesia for caesarean section.

Keywords: Parturient, Cardiac Output, Heart rate, Systemic vascular resistance.

Introduction

Subarachnoid block is anaesthesia of choice for caesarean section because of its well known advantagesover general anaesthesia [1,2].These advantages are offset by post-spinal hypotension reported in 50-90% of theparturientif appropriate preventive measures are not taken.[3,4] Prevention and treatment of this complication, has been an important issue for both anaesthesiologists and obstetricians.A variety of methods including physical manoeuvres(compression stockings, left uterine displace-ment), intravenous fluid expansion, and prophylactic use of sympathomimetic drugs [5, 6]have been used to prevent post-spinal hypotension.Phenylephrine is widely considered as vasopressor of choice for the treatment of spinal hypotension. [6,7] Phenylephrine is an alpha adrenergic agonist. It increases systemic vascular resistance (SVR), decreases heart rate (HR) and cardiac output (CO), andhas faster onset of action.[8]Although adverse effect of phenylephrine induced decrease in HRand CO in healthy patients with unstressed foetus is not known, but there may be potential for harm in the presence of a compromised foetus.[9]So vasopressors with less pronounced reflex negative chronotropic effects is of interest.We postulated that norepinephrine which isa potent α-adrenergic receptor agonist with relatively weak agonist action on β-adrenergic receptors, might thereforebe an effective vasopressor for maintaining blood pressure during spinal anaesthesia with lesser tendency to decrease HR and CO compared with phenylephrine.In present study we compared prophylactic computer controlled infusion of phenylephrine and norepinephrine for prevention of hypotension in parturient undergoing spinal anaesthesia for elective caesarean section. We assessed CO asprimary outcome and HR, MAP, SVR, SV, neonatal Apgar score and umbilical cord blood gas analysis as secondary outcomes.All previous studies have used technique of non-invasive haemodynamic monitoring but in present study, we have done minimally invasive monitoring so as to give continuous measurement of MAP, SVR, CO, and better understanding of haemodynamic changes during spinal anaesthesia for caesarean section.

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Material and method

With due approval from ethical committeeof our institute (F.1/Acad/MC/JU/17/1473, 23.01.2017) a prospective, randomized, comparative study was done on 86 pregnant females from January 2017 till completion of the desired number of cases in Janana wing of our hospital. (CTRI No /2017/09/009638). In this study parturient planned for elective caesarean section were randomly selected in the obstetrics ward. Eighty sixparturient belonging to ASA class I and II with singleton pregnancy at term scheduled for elective caesarean section under spinal anaesthesia between age of 18-40 years, with height ranging from 140 to 180cms and weighing between 40 to 80 kg were included in the study. The exclusion criteria were emergency caesarean section, active labour, all contraindications of central neuraxial block, high risk pregnancy, any comorbidity, foetal abnormality, patient taking MAO inhibitors or tricyclic anti-

depressants, patients allergic to any medicationsused in the study.A written informed consent was obtainedand a detailed pre anaesthetic check-up(PAC) was done a day before surgery. On entering the operation room, identification of patient was done and fasting status, consent, PAC were checked. Routine antacid prophylaxis was given. Patient was positioned on the operating table in the supine position with left lateral tilt and standard monitoring were applied. A large-bore intravenous cannula was inserted into a forearm vein under local anaesthesia, but no pre-hydration was done. Under all aseptic precautions a 22 gauge arterial cannula was inserted in radial artery after local infiltration of 1% lidocaine (w/v). Arterial line was connected with Flo Trac sensor cardiac output monitor (Edward's Lifescience Vigileo Monitor, Irvine, CA92614-5686 USA) for CO, SVR monitoring. A Peripherally Inserted Central Catheter (PICC) line was secured under all aseptic precautions in the right cephalic vein under local anaesthesia and CVP was obtained by multipara monitor and CVP so obtained was fed in CO monitor to derive SVR every time. After a brief settling period, HR and SPO2 were recorded by using an automated multipara monitor. SV, CO and SVR were recorded by Cardiac Output Monitor[10].These parameters were cycled every 1 to 2 min until three consecutive recordings with a difference of not more than 10%. The mean values of these parameters were calculated and defined as baseline values. A separate written consent was taken for arterial line and PICC before insertion. All parameters were recorded by the same experienced operator, who was blinded to the group assignment. Spinal anaesthesia was administered to all patients in sitting position, using full aseptic precautions. After skin infiltration with lidocaine 1% (w/v), a 25-gauge Quincke's spinal needle was inserted in the L3-L4 or L4-L5 intervertebral space. After confirmation of free flow of cerebrospinal fluid, 2 ml of hyperbaric bupivacaine 0.5% (w/v) with 25 µg fentanyl was injected intrathecally, and the patient was positioned supine with 10-15 degreeshead low tiltAt the time of intrathecal injection, rapid intravenous co-hydration with lactated Ringer's solution was commenced. From the time of intrathecal injection until delivery, the vasopressor infusion was regulated by using a computer-controlled closed-loop feedback system.[11,12] The infusion was initially commenced at a fixed rate of 30 ml/hr. After the completion of the first blood pressure measurement after spinal injection, the infusion was regulated to maintain MAP according to the following algorithm

$$\text{Infusion rate ml / hr} = (10 - \text{error \%}) \times 3 \quad (1)$$

where error% = (measured MAP– baseline MAP)/baseline MAP× 100

The patients were randomly allocated into one of the two predefined groups by chit in box method. The person who prepared the drug solutions was different from the person who administered the drugs and collected the data intra-operatively. According to the randomization code, a solution of either norepinephrine 5 µg/ml (Group N) or phenylephrine 100 µg/ml(Group P) was chosen. The drugs were prepared by careful dilution in normal saline in 50 ml syringes that were labelled "study drug". The randomization code was not revealed until after recruitment of the final patient in the study(concealment).

Group P (n=40) Received infusion of inj. phenylephrine 100 µg/ml IV.

Group N (n=40) Received infusion of inj. norepinephrine 5 µg/ml IV.

The infusion rate was within the limits 0 to 60 ml/h (0 to 5 µg /min of norepinephrine and 0 to 100 µg /min of phenylephrine). Infusion of the study drug was stopped immediately, if the HR fell below 50 beats/min. The total volumes of vasopressor solution given uptothe time of uterine incision and upto 30 min after starting drug infusion were recorded. NIBP, HR,CO, SV and SVRwere monitored at 1 min after intrathecal injection, then at 3 min and thereafter every3 min up to 30 min. Then infusion was stopped and all parameters were recorded at 5min interval up to 45 min and then at 15 min interval up to 2 hours. The incidence of hypotension (defined as fall in MAP greater than 20% from baseline), hypertension (defined as rise in MAP greater than 20% from baseline), and bradycardia (defined as HR <60 beats/min) were recorded. Episode of bradycardia was managed with administration of inj. atropine 0.6mg IV.The levels of sensory and motor blockade were assessed, the highest level of blockade was recorded. If adequate level of block was not achieved (T5), general anaesthesia was given and case was excluded from the study. Surgery was allowed to commence when the attending anaesthesiologist considered the block to beadequate. Supplemental oxygen was givenwhen SpO2fell below 95%. Apgar score was assessed by a midwife at 1 and 5 min after delivery. Samples of umbilical arterial (UA) and umbilical venous (UV) blood were collected from a double-clamped segment of umbilical cord for blood gas analysis.

Sample size calculation

The sample size was calculated at 95% confidence interval and 80% power assuming the difference in mean cardiac output (primary outcome) between the two groups to be 9% and pooled standard deviation 14% [13]Calculated minimum sample size was 38 subjects in each group which was increased to 43 subjects in each group considering 10% attrition.

Null Hypothesis H0- There is no difference in cardiac output between phenylephrine and Norepinephrine when used for prevention of hypotension in parturient.

Statistical analysis

Data were tested for normality by using unpaired Student *t* test as appropriate. Nominal data were compared by using the Chi-square test or Fisher exact test. Analysis was performed using Microsoft Excel 2010, IBM SPSS Statistics version 20 (trial version).Value of *P* less than 0.05 was considered statistically significant.

Results

Hundred patients were assessed for eligibility.Eighty six were randomized (43 in each group). Their randomization, allocation, follow-up and analysis are given in CONSORT flow diagram (Fig1). Finally 40 patients were analysed in each group.Patients characteristics, gestational age, level of dermatomal block, duration of surgery, duration of anaesthesia, total fluid given during surgery were comparable in both the groups and no statistically significant differences were observed between the study groups (Table1).

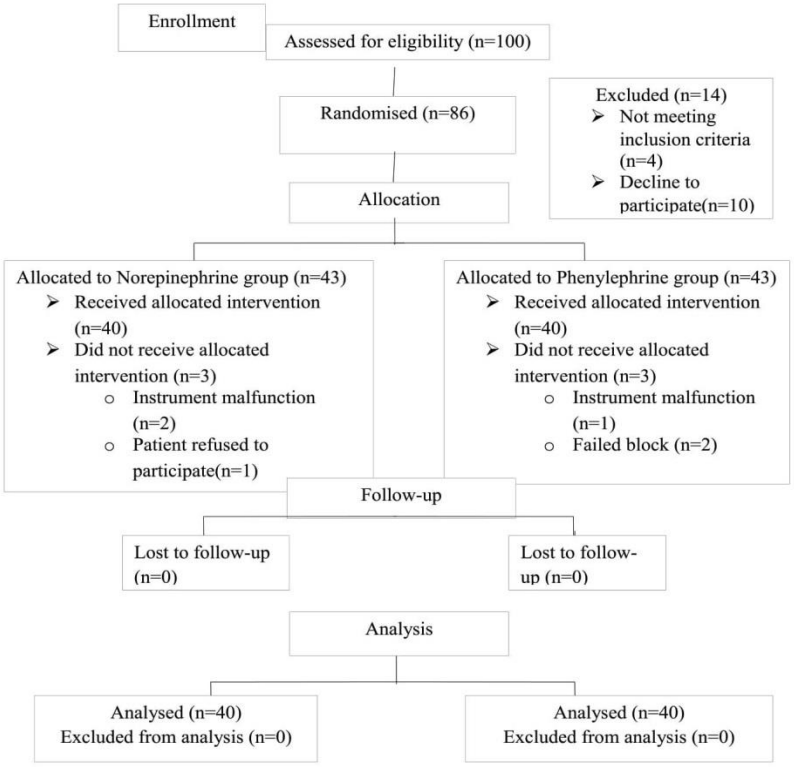

Fig 1:CONSORT diagram

Table1: Summary of demographic characteristics and intra-operative variables

Parameter	GROUP N	GROUP P	P-value
Age(years)(Mean±SD*)	24±4.5	22±6.5	0.12
Weight (kg)(Mean±SD)	59.57±6.33	59.60±6.33	0.986
Height (cm)(Mean±SD)	151.37±3.94	150.37±3.67	0.244
ASA I	19 (47.5%)	21 (52.5%)	0.832
ASA II	21 (52.5%)	19 (47.5%)	0.832
Gestational age (weeks) Median (range)	38 (36-39)	38 (36-39)	1.0
Upper sensory level, Median (range)	T5 (T3-T6)	T5 (T3-T6)	1.0
Duration of surgery(min)(Mean±SD)	50.40±7.60	52.70±6.50	0.82
Total fluid during anaesthesia(ml)(Mean±SD)	1800±100	2000±150	0.75

***SD- Standard deviation. Group N= Norepinephrine group, Group P= Phenylephrine group**

There was significant difference found in cardiac output between the groups at 1st min (group N =6.96±1.82 and group P=6.17±0.99, p=0.01), at 3 min (group N =7.44±1.40 and group P=5.67±1.15, p<0.0001), at 6 min (group N =7.36±1.50 and group P=6.23±2.07, p=0.006) and 9 min (group N =8.12±1.66 and group P=6.71±2.0, p=0.001). Higher cardiac output was found in group N compared to group P. Rest of the time cardiac output was comparable in both the groups (Fig 3). There was significant difference in heart rate found in both the groups at 1st min (group N =102.37±13.68 and group P =89.35±16.78, P=0.0003), 3 min (group N=93.90±16.50 and group P=68.80±10.53,P<0.0001) 6 min(group N=84.80±11.94 and group P=67.37±10.83,P<0.0001) 9min(group N=84.12±15.03 and group P=69.30±13.00,P<0.0001) and 12 min (group N=83.10±13.45 and group P=75.62±13.32 p=0.0078) group P had lower HR in comparison to group N. (Fig 2). For group N the confidence interval for 95% was 1.34 (range 80.70-83.39) and for group P was 1.64 (range 80.36-83.64) which are almost overlying each other, resulting in no significant difference in MAP between the groups in time interval up to 2 hours. (p>0.05) (Fig 4)

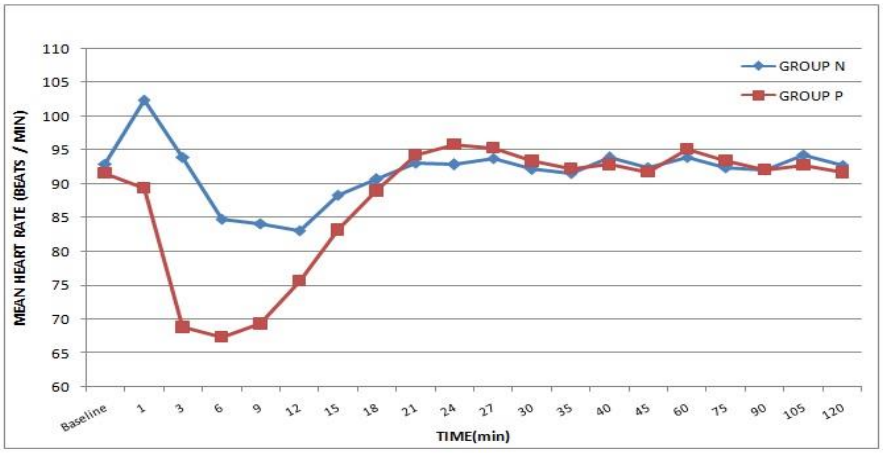

Fig 2:Mean heart rate(beats/min) in both groups.Groups N=Norepinephrine group,Group P=Phenylephrine group

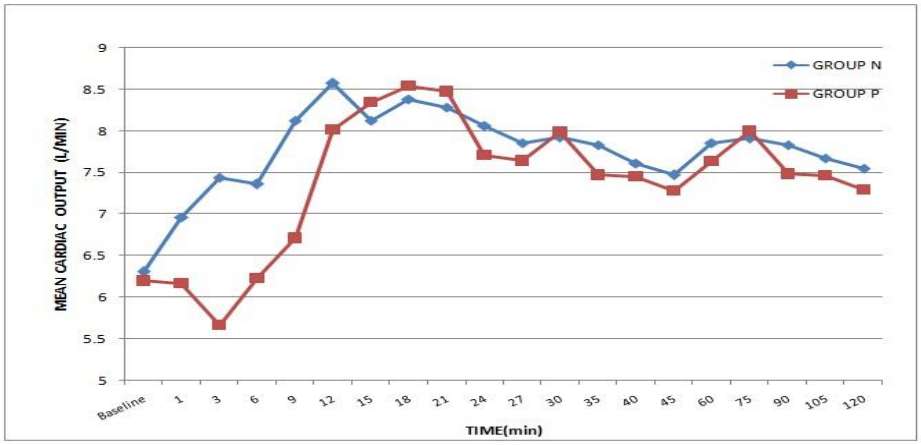

Fig 3:Mean Cardiac output (L/min) in both groups.Groups N=Norepinephrine group,Group P=Phenylephrine group

No significant difference was found between the groups throughout the two hour period in SV (p>0.05) (Fig 5). Significant difference in SVR was found between the two groups at 6min(P=0.004), 9min(P=0.001) and 12 min (P=0.05). SVR was more in group P in comparison to group N. (Fig 5).

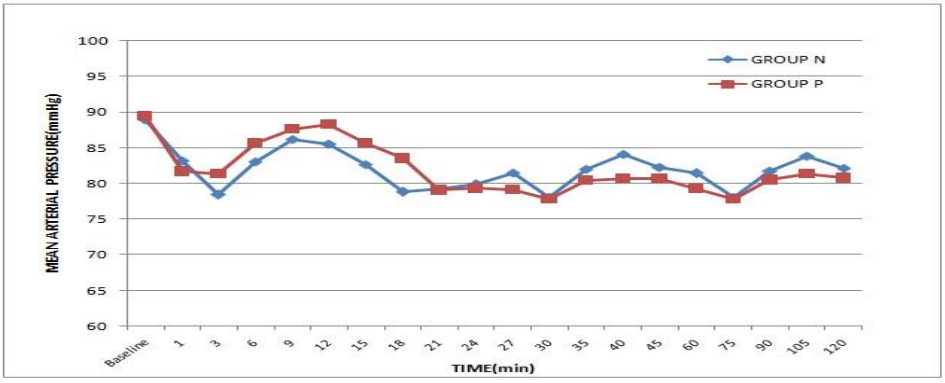

Fig 4:Mean arterial pressure (MAP,mmHg).Groups N=Norepinephrine group,Group P=Phenylephrine group

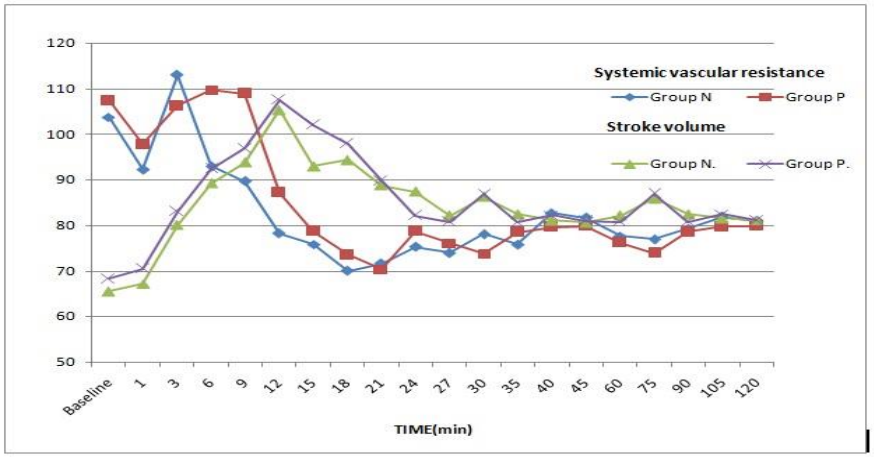

Fig 5:Systemic vascular resistance (SVR,KPa-s/l) and stroke volume(SV,ml).Groups N=Norepinephrine group,Group P=Phenylephrine group

Total volume of vasopressor infusion required for maintaining blood pressure up to the time of uterine incision was significantly higher in group N in comparison to group P(group N=2.83±0.46 and group P=2.59±0.50,P=0.03) and also significantly higher in group N compare to group P up to 30 min(group N=16.82±2.54 and group P=14.26±1.82,P<0.0001).(Table2)Birth weight and Apgar scores were comparable in both the groups (p=0.459 and p=0.815 respectively) (Table2). There was no significant difference found in umbilical blood gas analysis between the groups(p>0.05)(Table3)

Table 2: Total volume of vasopressors up to uterine incision and up to 30 min, Apgar score and birth weight

Parameter	GROUP N(mean ±SD*)	GROUP P(mean ±SD*)	P value
Total volume of vasopressor up to uterine incision (ml)	2.83±0.46	2.59±0.50	0.03
Total volume of vasopressor up to 30min (ml)	16.82±2.54	14.26±1.82	<0.0001#
Birth weight (kg)	2.92±0.303	2.86±0.32	0.459
APGAR score at 1 min	8.97±0.15	9.0±0.00	0.0751
APGAR score at 5 min	9.35±0.48	9.32±0.47	0.815

***SD- Standard deviation. # significant p value(p<0.05), Group N= Norepinephrine group, Group P= Phenylephrine group**

Table 3: Changes in foetal umbilical blood gas parameters in both the groups

Blood gas parameters	Umbilical artery blood gas values			Umbilical vein blood gas values		
	Group-N(N=40)	Group-P(N=40)	P value	Group-N	Group-P	P value
pH	7.23±0.02	7.23±0.028	0.824	7.28±0.03	7.27±0.02	0.972
PCO_2(mm Hg)	49.93±2.34	49.58±2.10	0.494	45.71±2.31	45.51±2.12	0.688
PaO_2(mm Hg)	22.06±4.20	21.77±4.44	0.761	32.52±4.46	32.07±4.55	0.656
Base Excess(mEq/L)	5.73±1.31	5.53±1.35	0.498	5.77±1.26	5.53±1.32	0.414
Hemoglobin(g/dl)	13.38±2.34	13.70±2.37	0.543	13.38±2.34	13.70±2.37	0.543
SPO_2(%)	26.62±7.19	25.65±7.59	0.557	52.98±7.41	51.78±7.92	0.486
Oxygen content (ml/L)	4.79±1.32	4.73±1.41	0.857	9.75±2.10	9.72±1.99	0.947

SD- Standard deviation.Group N= Norepinephrine group, Group P= Phenylephrine group

In our study one patient had complain of nausea and vomiting in group N and inj. ondansetron 4mg IV was given. One patient of group N required supplemental oxygen because saturation was < 95%. In group P vasopressor infusion was stopped in two patients because HR fell below 50/min. These data were statistically non-significant.

Discussion

Studies using minimally invasive cardiac output monitors have demonstrated that after induction of spinal anaesthesia there is marked reduction in SVR with compensatory modest increase in CO, HR and SV.[8,14] Sovarious investigators have started to use vasopressor regimens for preventing spinal hypotension. Vasopressors like ephedrine, phenylephrine, methoxamine, dopamine, mephenteramine have been used to maintain haemodynamic after spinal anaesthesia.[15,16]In this study we have compared prophylactic computer controlled infusion of phenylephrine and norepinephrine for prevention of hypotension in parturient undergoing spinal anaesthesia for elective caesarean section.In our study CO was higher in group N from 1 to 9 minute in comparison to group P. After this no significant difference was

found. The CO maintenance by norepinephrine is mainly due to its positive chronotropic effects. However, it is possible that a positive effect of norepinephrine on venous return may also have contributed to maintain CO. In non-obstetric patients, it has been shown that pure α-adrenergic agonists can increase venous return by constricting capacitance vessels, but this may be opposed by an increase in venous resistance which can reduce venous return.[17] However, veins also have β-adrenergic receptors, and norepinephrine has been demonstrated to constrict capacitance vessels without an increase in venous resistance.[17,18]The CO results of our study are consistent with similar studies by Ngan Kee et al[13]who found normalized CO greater at 5 min in the norepinephrine group compared with that in phenylephrine group(median 102.7% v/s 93.8%, p=0.004, median difference 9.8%, 95 CL of difference between medians 2.8 to 16.1%) and Stewart A et al[9]showing that phenylephrine has a dose-related tendency to decrease CO. Dyer A et al[8]compared the effects of bolus phenylephrine and ephedrine on maternal cardiac output in spinal anaesthesia for caesareansection also foundthat mean CO values were significantly lower after phenylephrine administration compared to ephedrine (P = 0.001). In our study we found that both vasopressors had similar efficacy to maintain SV. These finding suggested that greater CO in norepinephrine group is mainly due to greater HR.We measured CO and SVR using EDWARD VIGILEO monitor with flotrac system. In this technique radial arterial cannulation isrequired for CO monitoring and a PICC line isrequired for SVR measurement. This technique does not require expertise like in non-invasive supra sternal Doppler method, gives accurate results inobese patients gives true value of CO and does not require normalization of values. This technique is based upon pulse contour analysis of arterial BP, gives reliable information of rapid short lasting changes in systolic BP, CO and SVR. Eldrid Langesaeter et al also did the continuous invasive monitoring of BP, SVR and CO in healthy pregnant women [14]Ngan Kee et al [13] used non-invasive supra sternal Doppler method which isreliable in younger patients only. [2]This technique depends on an estimation of aortic valve cross-sectional area that is determined using an algorithm based on patients' height, thus it introduces potential for systematic error in the derivation of absolute values.After starting the vasopressor infusion there was a greater decrease in HR in group P in comparison to group N from base line values. Above findings denote that the use of pure α-adrenergic drugs such as phenylephrine have a dose-related tendency to decrease HR. Using drugs that also have mild β-adrenergic receptor activity in addition to potent α-adrenergic receptor activity such as norepinephrine will not decrease HR to that extent. The results obtained in present study are consistent with that ofNgan Kee et al [13] and Stewart A et al[9].Ngan Kee et al found greater HR in norepinephrine group compared with that in phenylephrine group (p=0.039). Stewart et al found that phenylephrine causes dose dependant decrease in HR and CO in parturient.Our study shows that norepinephrine and phenylephrine have similar efficacy for maintaining maternal MAP during spinal anaesthesia for caesarean section, suggesting that norepinephrine can be used for spinal hypotension instead of phenylephrine. In the present study, after starting the vasopressor infusionSVR was significantly higher in group P in comparison to group N at 6, 9 and 12 min. Norepinephrine and phenylephrine both are potent α1-agonist, have ability to constrict capacitance vessels and increase systemic vascular resistance but norepinephrine also has some β agonist activity and thus lower efficacy to increase SVR in comparison to phenylephrine. This is also shown by other studies.[8,13]Total volumes of infusion required for maintaining MAP pressure up to the time of uterine incision and upto30 min after starting drug infusion were more in group N in comparison to group P.We compared norepinephrine at a concentration of 5 µg/ml versus phenylephrine at 100 µg /ml according to our estimate of potency ratio of 20:1. This ratio has been used in previous clinical comparisons of norepinephrine and phenylephrine.[20,21] Our estimate of potency was based on previously reported work by Sjöberg et al[22] who compared the effects of norepinephrine and phenylephrine according to the drugs' vasoconstrictor activity alone. Further work is required to determine the relative potencies of norepinephrine and phenylephrine used to maintain blood pressure in obstetric patients.Stewart A et al[9] found significant difference in concentration-dependent effects on the duration of the infusion, infusion dose, and total dose received (linear trend; P = 0.05). The lower the concentration of phenylephrine, the longer was the infusion time, but with lower total dose.There was no effect of phenylephrine and norepinephrine on foetal outcomes like Apgar score and birth weight. Umbilical venous blood pH andumbilical vein oxygen content were greater in the group N which possibly may relate to greater placental blood flow and oxygen delivery in the group N. There is a possibility of decreased foetal stress in this group compared with the phenylephrine group. However, the differences were small and statistically not significant (p>0.05). Further work is required to confirm this observation and to determine whether norepinephrine may have any clinical advantage, for example, in patients with preeclampsia or in other conditions in which uteroplacental circulation may be compromised. The results obtained in the present study are similar to those of Ngan Kee et al.[13,23,24. In a similar study, Ahmed et al[25] compared phenylephrine and norepinephrine and observed the incidence of post spinal hypotension and bradycardia in both groups.While our study is more extensive as in addition to above observations,we observed the effect of both the drugs on CO, SV and SVR of the parturient.We have also noted Apgar score and umbilical blood gas parameters.Umbilical blood gas parameters were different in both the groups but the difference was not statistically significant. Larger sample size may be required for further workup for evaluating beneficial effects of norepinephrine in stressed foetus.

Conclusion

Norepinephrine had greater efficacy for maintaining CO and similar efficacy for maintaining MAPin comparison to phenylephrine during spinal anaesthesia for caesareansection.

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