EFFICACY OF A COMBINATION OF PREEMPTIVE PHENYLEPHRINE WITH CRYSTALLOID PRELOADING IN SPINAL ANAESTHESIA HYPOTENSION- A PROSPECTIVE, RANDOMISED, DOUBLE-BLIND STUDY

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ABSTRACT

BACKGROUND

Hypotension is the most common adverse effect of spinal anaesthesia and contributes to increased perioperative morbidity. Experts differ in their opinion as to the most effective method of managing this complication. We evaluated the efficacy of combining prophylactic Intramuscular (IM) phenylephrine with crystalloid preloading as against crystalloid preloading alone to prevent or reduce the severity of hypotension in patients undergoing subarachnoid block for elective abdominal hysterectomy.

MATERIALS AND METHODS

In this prospective double-blind study, 60 patients undergoing elective abdominal hysterectomy were randomised into two equal groups (groups PP and PC). After preloading with 10mLkg^{-1} balanced salt solution, group PP received preemptive IM phenylephrine 3mg while group PC received 2 mL IM normal saline as placebo, both given immediately after induction of spinal anaesthesia. Baseline and perioperative systolic, diastolic, Mean Arterial Pressures (MAP) and Heart Rate (HR) were recorded and compared. The incidence of hypotension, total number of episodes of hypotension, the requirement of rescue vasopressor and occurrence of any adverse effects were also noted.

RESULTS

Data were analysed using Student's unpaired t-test, Fischer's test and ANOVA tests. Though the incidence of hypotension was comparable in both groups, the severity of hypotension as assessed by the total number of hypotensive episodes (P 0.009), the percentage reductions in MAP (P 0.013) and the mean dose requirement of ephedrine (p0.002) was significantly lower in group PP when compared to group PC.

CONCLUSION

Combining 3 mg prophylactic IM phenylephrine with crystalloid preloading is safe and effective in improving haemodynamic stability following spinal anaesthesia.

KEYWORDS

Spinal Anaesthesia, Hypotension, Intramuscular, Phenylephrine, Preloading, Hysterectomy.

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BACKGROUND

Spinal anaesthesia is often used for abdominal hysterectomies as it offers a profound and high quality sensory and motor blockade. The most common side effect of this anaesthetic technique is hypotension with a varying incidence ranging from 30 to 80%.[1] Hypotension during spinal anaesthesia results mainly from blockade of the sympathetic nervous system, which leads on to a decrease in systemic vascular resistance and cardiac output. Intraoperative hypotension has been variously implicated with multiple perioperative adverse sequelae like myocardial ischaemia, acute kidney injury, stroke and increased 30-day mortality.[2,3,4]

Even after years of evolution of spinal anaesthesia, there has been no definite protocol either to prevent or to manage this complication. The various measures employed include preloading or co-loading with crystalloids or colloids, use of short-acting vasopressors either given prophylactically or as a part of management protocol, table tilt, leg binders and compression devices.[5] Given the frequency with which intraoperative hypotension occurs and its adverse consequences, it would be more logical to be proactive rather than reactive.[6]

Crystalloid preloading is one of the commonest methods used in this clinical setting and is the routine practice employed in our institution.[7] The goal of preloading is to increase venous return and preserve central blood volume and cardiac output. An alternative approach to this is the administration of preemptive

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vasopressors in the form of Intramuscular (IM) depot injection as suggested by a number of recent authors.[8,9,10]

Phenylephrine, a pure α-adrenergic agonist, whose action is expected to counteract the decrease in systemic vascular resistance induced by spinal anaesthesia without increasing the heart rate has been found to be effective when given intramuscularly.[8] Current literature supports the use of phenylephrine as the vasopressor of choice in spinal anaesthesia hypotension.[9]

There have been various studies in literature comparing different prophylactic regimes for spinal anaesthesia hypotension.[10] Key researches in this context often focus on obstetric anaesthesia and compare various Intravenous (IV) prophylactic regimes.[11] The latest Cochrane review on spinal hypotension opined that future research be directed towards using a combination of interventions rather than a single technique.[6]

In this prospective, randomised, double-blind study, we hypothesised that combining preemptive IM phenylephrine with crystalloid preloading would be safer and more effective in preventing spinal hypotension than preloading alone.

MATERIALS AND METHODS

The study was approved by the institutional research and ethics committee. After obtaining written informed consent, 70 American Society of Anaesthesiologist (ASA) I patients scheduled for elective abdominal hysterectomy under subarachnoid block were randomised by means of random number chart into two groups, Phenylephrine Preload Group (PP) and Preload Alone Group (PC). Patients who were unwilling, having hypertension or any significant medical illness, otherwise contraindicated for spinal anaesthesia, those allergic to local anaesthetics or any other drug and obese patients (BMI >29) were excluded from the study.

All patients were advised preoperative fasting for eight hours. Each patient received oral ranitidine 150mg and metoclopramide 10mg at 6 a.m. on the morning of surgery. A 16 gauge Intravenous (IV) cannula was cited in the nondominant hand introduced under local anaesthesia and midazolam 1mg was administered intravenously. The baseline pulse rate, systolic and diastolic blood pressures were determined from the average of three consecutive readings at two-minute intervals to alleviate the effects of anxiety. All patients received 10mL/kg of balanced salt solution as preload infused rapidly over 15 to 20 minutes just prior to the subarachnoid block. In the theatre, subarachnoid block was performed under standard monitoring at L3-4 interspace using 25G Quincke needle and 3.4mL (17mg) 0.5% bupivacaine was given. After completion of injection, patients were immediately made supine and the IM injection of the study medication was given in the anterolateral thigh. This comprised of 3 mg phenylephrine made up to 2mL in group PC and 2mL normal saline in group PP and was administered by an anaesthesiologist not involved in the care of the patient or collection of data. A second anaesthesiologist blind to the identity of the study medication, monitored and managed the patient. Thus, double blinding was ensured throughout the study. Oxygen was administered with simple face mask at a rate of 5 litres/minute to all patients till the end of surgery.

The time of IM injection was taken as time zero. Block height was assessed by pinprick discrimination at 5 and 20 minutes after blockade. After subarachnoid injection, 4mL/kg of balanced salt solution was given intravenously over 20 minutes and a maintenance infusion of the same crystalloid was then run at a rate of 4mL/kg/hour throughout surgery. In addition to the loading dose of IV fluids, patients received additional fluids as deemed necessary.

Pulse rate, systolic and diastolic arterial pressures were recorded at 2 minutes intervals for the first 20 minutes and thereafter at 5 minutes intervals till the end of surgery and at 5 minutes intervals after surgery for 30 minutes.

Hypotension was defined as Systolic Arterial Pressure (SAP) of <90 mmHg or a decrease of more than 25% from the baseline Mean Arterial Pressure (MAP). This was treated with rescue IV bolus doses of ephedrine 6 mg until the pressures reached above threshold values. The number of boluses and the time of the first ephedrine bolus were noted. Bradycardia defined as Heart Rate (HR) <50/minute was treated with Inj. Atropine 0.6 mg. Hypertension was defined as elevation of systolic BP by more than 30% from the baseline. Appropriate treatment was instituted if hypertension persisted beyond five minutes.

The outcome parameters noted were the incidence of hypotension, total number of episodes of hypotension, the time of first rescue vasopressor and the total dose required. The percentage changes in MAP and HR were calculated from the difference between the baseline and the lowest recorded MAP and HR, respectively. The occurrence of any adverse effects was also noted.

Statistical Analysis

The data collected from this prospective, randomised, double-blind study were entered into a master chart and necessary statistical tables were constructed. The statistical constants like arithmetic mean, standard deviation, percentage, etc. were computed to get valid inference about the data for comparison. In order to see whether the differences in estimates in the study groups were statistically significant, the Student's unpaired t-test and Fischer's exact proportions were applied. Individual unpaired t-test was applied for comparison of intraoperative haemodynamic parameters and the results were analysed using ANOVA test for comparison between groups and within groups. A P value of less than 0.05 was considered statistically significant.

RESULTS AND ANALYSIS

Out of a total of 70 patients enrolled, 60 completed the study (Figure 1). The patients in both groups were comparable with respect to age, height, weight, dermatomal sensory levels at 20 minutes after blockade

and duration of surgery (Table 1). Baseline haemodynamic parameters were also comparable.

Variable	Group PP (n=30)	Group PC (n=30)	P value
Age (year)	45.63 (5.37)	46.87 (4.58)	0.342
Height (cm)	155.2 (2.77)	155.03 (4.10)	0.854
Weight (kg)	54.33 (5.29)	54.20 (4.99)	0.920
Block height	$T_6(T_4\text{-}T_6)$	$T_6(T_4\text{-}T_7)$	0.572
Duration of surgery (mins.)	75.333(17.515)	67.33 (17.55)	0.082

Table 1. Demographic Profile

Data expressed as mean (SD), except sensory block height as median (range).

Variables	Group PP	Group PC	P†value
Incidence of hypotension*	18 (60%)	22 (73%)	0.584
No. of episodes of hypotension	54	115	0.009
Time to first ephedrine (mins.)#	14.5 (4.12)	23.11 (14.71)	0.06
Dose of rescue IV ephedrine (mg)#	1.4 (3.76)	6.4 (7.55)	0.002

Table 2. Analysis of Hypotensive Episodes

*Number of patients (%); †P value<0.05 significant; #Data expressed as mean (SD).

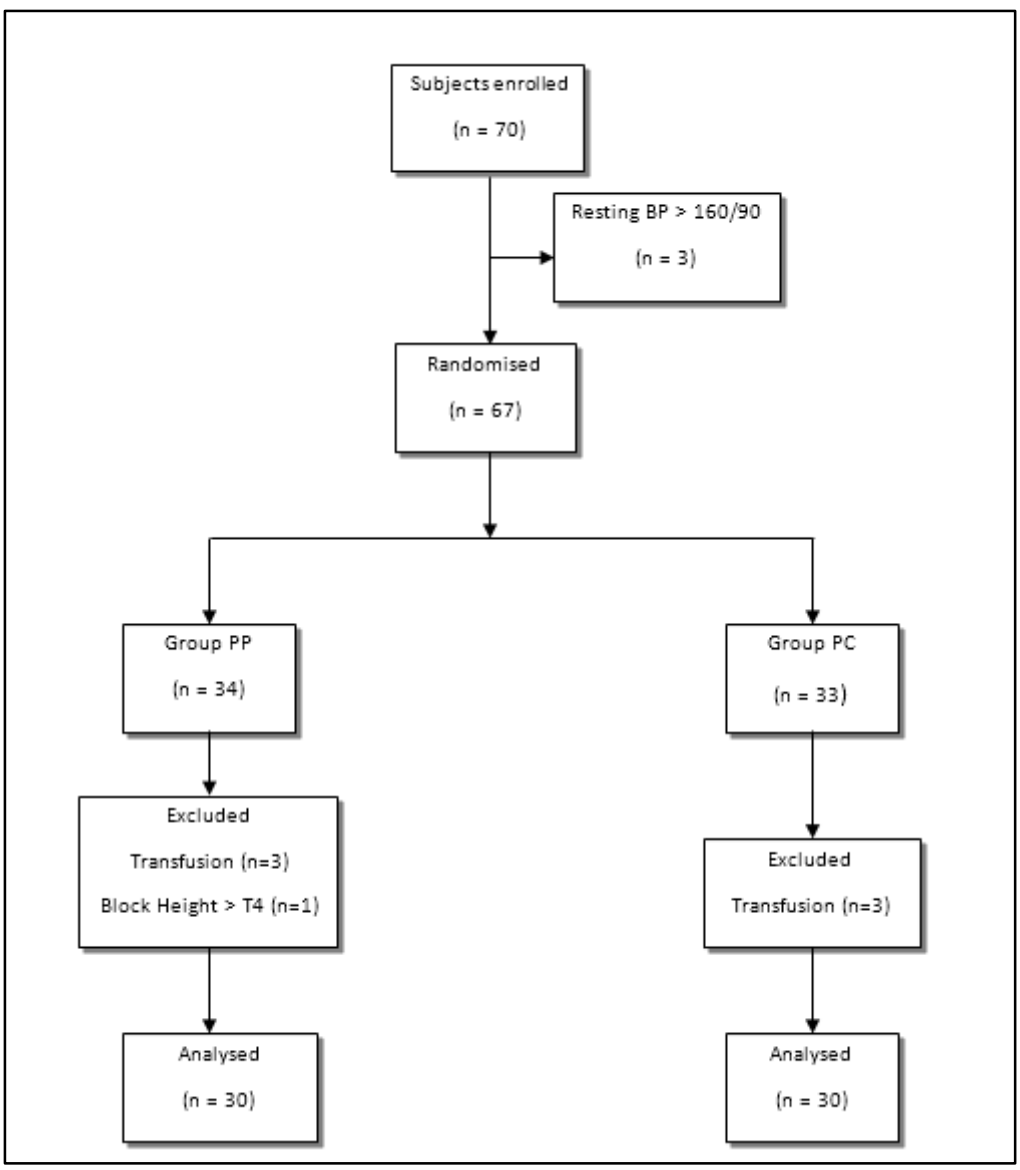

Figure 1. Consort Flow Diagram

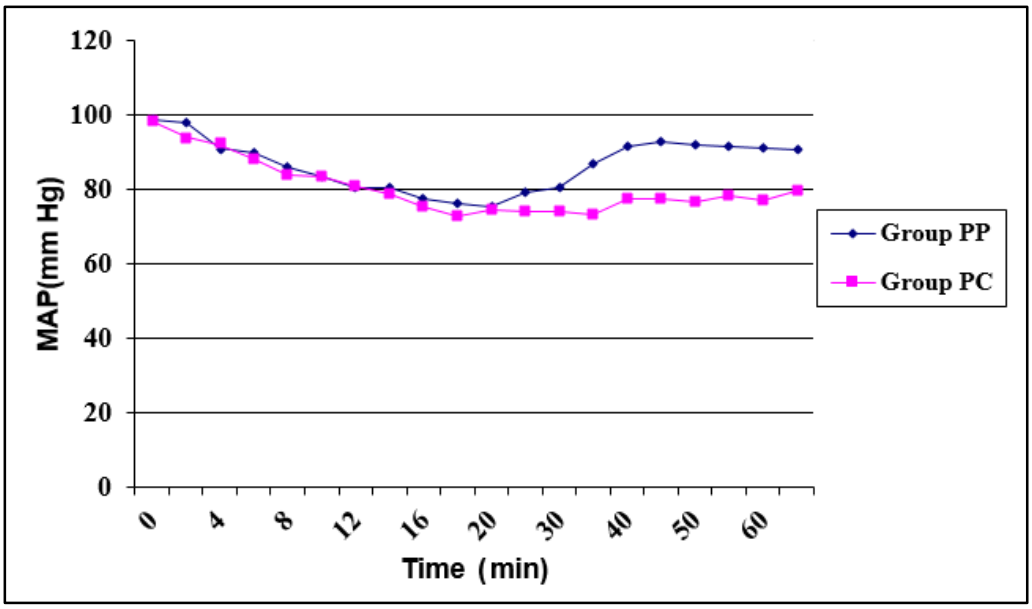

Figure 2. Comparison of Intraoperative Map

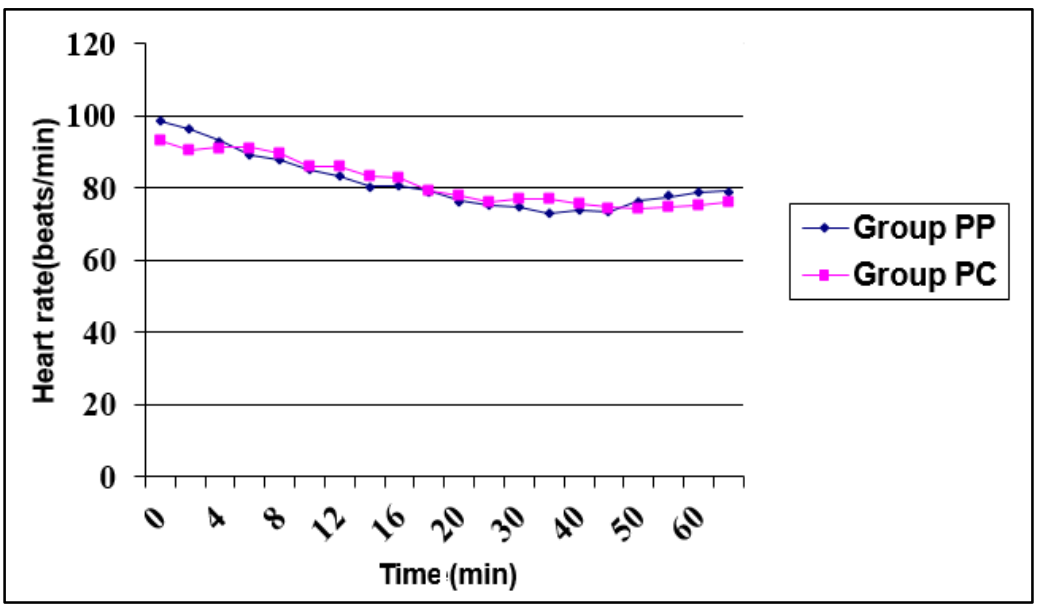

Figure 3. Comparison of Intraoperative Heart Rates

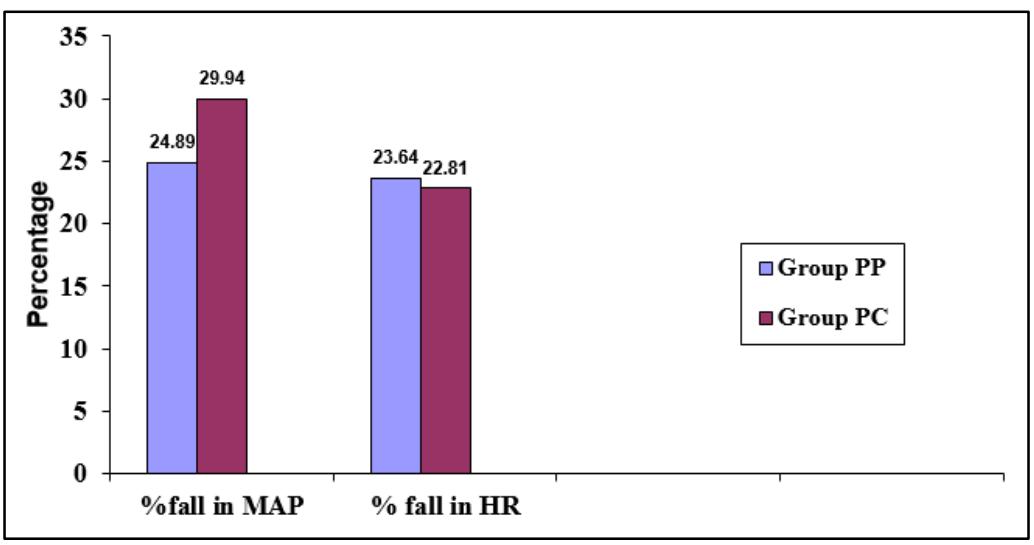

Figure 4. Percentage Reduction in MAP and HR from Baseline

The incidence of hypotension (defined as the number of patients who developed hypotension) and the total number of episodes of hypotension in the two groups were compared using the Fischer's exact test. Eighteen patients (60%) in group PP and 22(73%) in group PC developed hypotension. This difference was not found to be statistically significant (P=0.584). But, there was a significant difference in the total number of episodes of hypotension in both groups. In the phenylephrine preload group, there were 54 episodes of hypotension as opposed to 115 in the preload alone group. The calculated P value 0.009 was found to be highly significant (Table 2).

There was a significant difference in the mean dose requirement of rescue IV ephedrine (P value = 0.002). The mean dose of ephedrine requirement in PP and PC groups were 1.4 ± 3.76 mg and 6.4 ± 7.55 mg, respectively. The mean time to the first ephedrine rescue bolus did not show a statistically significant difference.

Individual unpaired t-test was applied for comparison of intraoperative haemodynamic parameters and the results were analysed using ANOVA test for comparison between groups and within groups. Intraoperative systolic blood pressures and MAPs between the two groups assumed significant difference from 25 minutes onwards with lower readings recorded in Group PC than in the Group PP (Figure 2). Heart rates were comparable in both groups throughout the study period (Figure 3).

The percentage decrease in MAP and HR of each subject were calculated from the difference between the baseline and the lowest recorded MAP and HR, respectively. Unpaired t-test was used for comparison between groups. Group PP had significantly lower percentage reductions in MAP (24.89± 6.86%) when compared to the group PC (29.94±8.36%), (P = 0.013). There was no significant difference in the percentage decrease in heart rate between the two groups (P=0.797) (Figure 4).

There was no statistically significant difference in incidence of hypertension between the two groups. The episodes of hypertension, which occurred in both groups did not last for more than 5 minutes and hence did not warrant any treatment. There were no episodes of bradycardia in either of the groups.

DISCUSSION

Cardiovascular side effects, principally hypotension and bradycardia are apparently the most important and most common adverse effects during spinal and epidural anaesthesia. The pathophysiology primarily includes a block-induced sympathectomy that leads on to a decrease in systemic vascular resistance.[12] Greatest magnitude of decrease in blood pressure occurs 15 to 30 minutes after initiating spinal anaesthesia.[13] Thereafter, there is a spontaneous increase of systolic blood pressure by about 5 to 10 mmHg over the next 10 to 15 minutes due to the compensatory mechanisms. Then, it remains more or less at a constant level, until the effect of the aesthetic on the nerve roots wear off. The ideal management of hypotension following subarachnoid block whether it is to be by fluid loading or by use of vasopressors or a combination of these two remains enmeshed in controversies.[14,15,16]

Traditionally, fluid loading as either preload or co-load was considered as the standard prophylactic regime for spinal anaesthesia hypotension while administration of vasopressors was more commonly considered for the treatment of hypotension. Many studies on type and timing of fluid loads have been undertaken, but only few of these studies have demonstrated a significant efficacy when given alone as a prophylactic regimen.[10,17]

The timing, route and type of vasopressor use have also been found to be different with various researchers. Most of the studies concentrate on IV prophylactic regimes and have been found to be safe and effective even in the elderly. But, these when given as a single bolus injection or infusion have limited duration of action when compared to the intramuscular route.[16] Continuous infusions need to be closely monitored and titrated according to blood pressure and requires the use of precise infusion pumps.[18]

Phenylephrine, a pure α_1 adrenergic agonist prevents spinal anaesthesia-induced hypotension by counteracting the decrease in systemic vascular resistance induced by spinal anaesthesia. Its effect is faster than that of ephedrine.[10] It is effective by both IM and IV routes and can be used for both prophylaxis and treatment of spinal hypotension. The timing of intramuscular administration to achieve optimum efficacy is difficult to predict. Pharmacokinetic studies have suggested that the peak effect of IM phenylephrine is 10 to 15 minutes after administration and maintains its effect for more than 60 minutes.[19]

Though the onset of subarachnoid block in our study occurred simultaneously with administration of the intramuscular vasopressor, we have demonstrated a reduction in the severity of hypotension as assessed by the number of episodes of hypotension and the requirement for rescue IV ephedrine boluses, but no difference in the time to first requirement for rescue IV ephedrine. This demonstrates that administering intramuscular phenylephrine immediately after the intrathecal injection is not too late to achieve a beneficial effect.

Gihan A.Gomaa et al in their study used 4 mg phenylephrine given IM 10 minutes before establishing spinal anaesthesia for elective caesarean delivery. They had a significantly lower incidence of hypotension 20% in the study group as opposed to 73% in the control group who received 1000 mL preload with normal saline alone without vasopressor.[20] However, giving IM vasopressors before a spinal aesthetic is more controversial because of concerns about reactive hypertension if the block fails. We delayed the administration of IM vasopressors until the induction of spinal anaesthesia because of these concerns.

Joachim O. Arndt et al studied the time course of arterial hypotension and/or bradycardia requiring treatment during spinal anaesthesia and concluded that crystalloid administration reduced side effects only during the first 15

minutes, whereas dihydroergotamine reduced those occurring more than 30 minutes after the start of anaesthesia.[21] This maybe because of the short half-life of crystalloids in the intravascular space. The poor efficacy of preloading alone in preventing hypotension was also proved by Rout et al.[15] They compared the use of no preload or 20 mL/kg crystalloid administered over 15 to 20 minutes before spinal anaesthesia and concluded that hypotension associated with spinal anaesthesia for caesarean section cannot be eliminated by volume preloading alone in a supine wedged patient.

The latest Cochrane intervention review on spinal anaesthesia hypotension concluded that no single method is effective in prevention of hypotension, but the incidence can be significantly reduced by a combination of various techniques.[6] Ngan Keeet al found that spinal hypotension was virtually eliminated by a combination of high-dose phenylephrine infusion and rapid IV crystalloid cohydration.[22]

In our study, we found that both the groups had comparable intraoperative haemodynamic parameters until 20-25 minutes after induction of spinal anaesthesia. After this period, the preload alone group had significantly lower systolic, diastolic and mean arterial pressures when compared to the phenylephrine preload group.

The patients who received IM phenylephrine with crystalloid preload demonstrated greater haemodynamic stability as evidenced by the significantly lesser episodes of hypotension, lower percentage reductions in MAP and total dose requirement of rescue ephedrine. These results are in agreement to similar studies conducted by various researchers.[8,16,23,24]

The incidence of hypotension though less in the group that received IM phenylephrine did not show a significant difference between the groups. A study by Kohki Nishikawa et al demonstrated that prophylactic injection of 1.5mg of phenylephrine IM is safe and effective for reducing the incidence of hypotension in surgical repair of hip fracture in normotensive and hypertensive elderly patients under spinal anaesthesia.[16] The mean dermatomal block height was T9 in this study. The incidence of hypotension was 13%, 7% and 73% in the normotensive 3 mg, 1.5 mg and control groups, respectively. The high incidence of hypotension (60%) noted in our study can be explained by the higher dermatomal level of sensory block required in our study (T6) as compared to the above-mentioned study. Using a higher dose of phenylephrine could probably reduce this incidence.

B.T.Ayorinde et al evaluated the efficacy of preemptive intramuscular phenylephrine given immediately after induction of spinal anaesthesia for elective caesarean section in 108 parturients. They found that 4mg phenylephrine reduced the severity of hypotension and total dose of rescue vasopressor.[8]

The second most important cardiovascular side effect of spinal anaesthesia is bradycardia. Blockade of cardiac efferent sympathetic fibres resulting in loss of chronotropic drive; reduced venous return, reduced right atrial filling and hence decreased outflow from the atrial stretch receptors (Bainbridge reflex) are the main factors contributing to bradycardia.[25]

Phenylephrine, a pure α_1 adrenergic agonist effectively restores systolic, diastolic and mean arterial pressures, but can produce reflex bradycardia and hence decreased cardiac output. A strong correlation between low heart rates and low Cardiac Output (CO) were found by many researchers.[26,27] Most of the studies on IV phenylephrine showed an increased incidence of bradycardia, especially with higher doses, whereas none of the studies on IM phenylephrine reported any significant bradycardia.[8,16,24,26,27] In our study, there was no incidence of bradycardia. The percentage decrease in HR from the baseline was similar in both groups (P value 0.797). The heart rates between the two groups were comparable throughout the study period. In our study, crystalloid preloading of 10 mL/kg was performed in the phenylephrine group. This moderate preloading may have contributed to the less incidence of bradycardia. Alternatively, the decreased incidence of bradycardia may have been because of a baroreceptor-mediated reflex tachycardia in response to the reduction in systemic vascular resistance after the induction of spinal anaesthesia. Ephedrine because of its overriding chronotropic effect and given as rescue vasopressor may have contributed to the lower incidence of bradycardia than would be expected with phenylephrine administration.

There was no statistical difference in the incidence of hypertension between the two groups. Since, these episodes did not persist beyond five minutes, no therapy was instituted.

Our study has few limitations. First, our study group comprised of only ASA1 normotensive patients, so we are not sure, if these data can be generalised for hypertensives also. Secondly, we avoided spinal additives to prevent the confounding adverse effect of bradycardia. But, nowadays pure bupivacaine spinal anaesthesia is rarely practiced. Colloid preload has been conclusively proven to be better than crystalloid. But, we followed our institutional practice for the comparison. Since, there are no universally accepted threshold values defining hypotension, it is difficult to compare the results of various studies. Finally, our results would have been more relevant, if we had used cardiac output monitoring. More research on various prophylactic combination techniques for spinal hypotension is recommended, so that an ideal guideline could be arrived at.

CONCLUSION

In summary, in this prospective, randomised, double-blind study, combination of preloading with balanced salt solution along with phenylephrine 3mg IM given immediately after subarachnoid block resulted in greater haemodynamic stability in normotensive patients undergoing elective abdominal hysterectomy when compared to administration of crystalloid preload alone.

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