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Evaluation of pre-emptive intramuscular phenylephrine 1.5mg and 3mg for reduction of hypotension induced by spinal anaesthesia in lower abdominal and lower limb surgeries

Raksha K Bairwa[1*], Raziuddin[2], Anju Garg[3]
[1] Consultant Anesthesia and Critical Care, DHRC, Jaipur, Rajasthan, India
[2] Senior Consultant Anesthesia and Critical Care, Metro Hopsital, Jaipur, Rajasthan, India
[3] Senior Consultant Anesthesia and Critical Care, DHRC, Jaipur, Rajasthan, India

Abstract
Aim: To evaluate pre-emptive intramuscular phenylephrine 1.5mg and 3mg for reduction of hypotension induced by spinal anaesthesia in lower abdominal and lower limb surgeries.
Material and Method: This prospective study was approved by our hospital's ethics committee and was conducted at medical trust hospital. The subjects included 90 patients aged older than 18 years (ASA physical status I–II) scheduled to undergo lower abdominal and lower limb surgeries under spinal anaesthesia. The patients were divided into 2 main group (45 each), hypertensive and normotensive. These groups were further subdivided into 3 subgroup, i.e. P-3 (phenylephrine 3mg), P-1.5 (phenylephrine 1.5mg), C (control). All medication with phenylephrine irrespective of the dose to be administered was made up to a volume of 2ml with 0.9% saline and administered to the patient. Standard monitoring included continuous electrocardiography and pulse oximetry. The percentage changes in MBP and HR was calculated from the difference between the baseline and the lowest recorded MBP and HR, respectively. No sedative medications were given during the procedure.
Results: The six groups were similar in age, weight, height and sex distribution as shown in above table ($p>0.05$). Episode of hypotension requiring treatment with ephadrin were higher in control (hypertensive and normotensive) group compared to P-3 (hypertensive and normotensive) group ($p<0.001$) and P-1.5 (hypertensive and normotensive) group ($p<0.001$).
Conclusion: Pre-emptive injection of intramuscular 1.5 mg of phenylephrine along with moderate fluid loading is a safe and effective method for reducing the incidence of hypotension associated with hyperbaric bupivacaine spinal anesthesia during lower limb and lower abdominal surgery, provided level of block is limited to lower thoracic segments.

Keywords: phenylephrine, hypertensive, normotensive, hypotension

Introduction
Spinal anaesthesia is often used for lower abdominal and lower limb surgeries. The most common complication of this anaesthetic technique is hypotension [1, 2], with a particularly frequent incidence in the elderly [3, 5]. This problem is a particularly important issue in elderly patients with cardiovascular disease such as hypertension, because their risk of ischemia secondary to hypotension is thus increased [6].
Regardless of the anaesthetic agent (drug) used, the desired effect is to block the transmission of afferent nerve signals from peripheral nociceptors. Sensory signals from the site are blocked, thereby eliminating pain. The degree of neuronal blockade depends on the amount and concentration of local anaesthetic used and the properties of the axon. Thin un-myelinated C-fibres associated with pain are blocked first, while thick, heavily myelinated A-alpha motor neurons are blocked last. The desired result is total numbness of the area. A pressure sensation is permissible and often occurs due to incomplete blockade of the thicker A-beta mechanoreceptors. This allows surgical procedures to be performed with no painful sensation to the person undergoing the procedure [4].
Phenylephrine is a selective α1-adrenergic receptor agonist used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Phenylephrine is used as a vasopressor to increase the blood pressure in unstable patients with hypotension. Such use is more common in anaesthesia or critical-care practices; phenylephrine is especially useful in counteracting the hypotensive effect of epidural and subarachnoid anaesthetics. It also has the advantage of not being inotropic or chronotropic, and so it strictly elevates the blood pressure without increasing the heart rate or contractility (reflex bradycardia may result from the blood pressure increase) [6].
The present study was conducted to evaluate pre-emptive intramuscular phenylephrine 1.5mg and 3mg for reduction of hypotension induced by spinal anaesthesia in lower abdominal and lower limb surgeries.

Material and method
This prospective study was approved by our hospital's ethics committee and was conducted at medical trust hospital. The subjects included 90 patients aged older than 18 years (ASA physical status I–II) scheduled to undergo lower abdominal and lower limb surgeries under spinal anaesthesia.

Inclusion Criteria
1. American Society of Anaesthesia physical status class I & II (ASA I - Healthy, ASA II - mild and controlled systemic disease)
2. Age ≥ 18 years.

Exclusion Criteria
1. Patients with coagulation defects or on anticoagulant

therapy, symptomatic coronary artery disease, cardiac valvular regurgitation or stenosis.
2. Patients with Neuromuscular disorders.
3. Patients not willing to undergo spinal anaesthesia.
4. Local infection at the site of subarachnoid injection.
5. Any other physical or psychiatric condition which may impair their ability to cooperate with study or data collection.
6. Pregnancy.

All the patients were randomized by sealed-envelope technique into one of the following 6 groups

a. Non hypertensive patients who received 3 mg of intramuscular phenylephrine (P-3.0 group).
b. Non hypertensive patients who received 1.5 mg of intramuscular phenylephrine (P-1.5 group).
c. Non hypertensive patients who received no medication (C group).
d. Hypertensive patients who received 3 mg of intramuscular phenylephrine (PH-3.0 group).
e. Hypertensive patients who received 1.5 mg of intramuscular phenylephrine (PH-1.5 group).
f. Hypertensive patients who received no medication (CH group).

All medication with phenylephrine irrespective of the dose to be administered was made up to a volume of 2ml with 0.9% saline and administered to the patient. No Patients received sedative premedication. Hypertensive patients on treatment were given their morning dose of antihypertensive medications. Before spinal anaesthesia, each patient received a rapid infusion of 8 mL/kg of lactated Ringer's solution over 20 min. Standard monitoring included continuous electrocardiography and pulse oximetry. Non-invasive arterial pressure (Systolic blood pressure [SBP], Diastolic blood pressure [DBP], and mean blood pressure [MBP]) and HR measurements were recorded at 3-min intervals for 30 min after the spinal anaesthesia and every 5 min thereafter for another 30 min by using an automated non-invasive BP monitor (Philips intelliVue MP40). The study lasted for 1 hour following drug administration, as the onset of pressor action after IM administered phenylephrine is usually within 10-15 minutes, and will last for approximately one hour.

Hypotension was defined as a decrease of more than 25% from the baseline MBP. Patients who met the criteria were treated with rescue IV bolus doses of ephedrine 6 mg until the MBP increased above the threshold level. Treatment with IV atropine 0.6 mg was given if bradycardia (defined as HR <50 beat per minute) occurred after the study medication. Hypertension (defined as a >20% increase in MBP from the baseline) after the study medication was to be treated with IV infusion of nitro-glycerine in titrated dose to achieve the goal. In addition to the loading dose of IV fluids, patients received additional lactated Ringer's solution as deemed necessary. The percentage changes in MBP and HR was calculated from the difference between the baseline and the lowest recorded MBP and HR, respectively. No sedative medications were given during the procedure.

Statistical analysis

The data was statistically analysed using SPSS software version 23. The collected data for the study were compiled and subjected to statistical analysis using student 't' test for comparison of demographic variables, X2 test for testing the significance of association between attributes and Two-factor ANOVA for comparison of mean blood pressure (MBP) and heart rate (HR) of the two groups under various time periods taken for the study.

Results

The patients were divided into 2 main group (45 each), hypertensive and normotensive. These groups were further subdivided into 3 subgroup, i.e. P-3 (phenylephrine 3mg), P-1.5 (phenylephrine 1.5mg), C (control). The six groups were similar in age, weight, height and sex distribution as shown in above table ($p>0.05$). The level of sensory block in the six groups were also comparable when analysed statically using X^2 test ($p=0.988$).

Table 1: Demographic characteristics of the patients under study

Variable	Hypertensive			NORMOTENSIVE		
	P-3	**P-1.5**	**C**	**P-3**	**P-1.5**	**C**
N	15	15	15	15	15	15
Age (years)	53.10±10.44	53.13±10.08	49.11±13.80	46.70±12.40	46.60±9.96	47.63±14.60
Height (cm)	167.10±3.56	166.11±4.03	167.00±5.39	166.00±4.58	169.00±4.35	168.00±4.00
Weight (kg)	65.33±5.69	63.00±3.76	64.50±4.26	62.11±4.97	62.20±4.35	63.90±6.60
Sex (M:F)	8:7	8:7	9:6	8:7	9:6	8:7
Level of block (Th)	10 (8-12)	10 (8-12)	10 (8-12)	10 (8-12)	10 (8-12)	10 (8-12)

P-3 = phenylephrine 3mg, P-1.5 = phenylephrine 1.5mg, C = control, M = male, F = female, Th = thoracic segment, n = number of patients, Mean ± SD.

The baseline mean blood pressure (MBP) were significantly higher in hypertensive group when compared to the normotensive group using student't' test ($p = 0.011$). However baseline mean blood pressure (MBP) was comparable between the three subgroup within the main group (hypertensive and normotensive). The baseline mean heart rate (HR) were significantly higher in normotensive group when compared to hypertensive group using student't' test ($p = 0.023$). Whereas baseline heart rate (HR) were comparable between the three subgroup within the main group (hypertensive and normotensive) as shown in table 2.

Table 2: Hemodynamic characteristics of the patients under study

Variable	Hypertensive			Normotensive		
	P-3	P-1.5	C	P-3	P-1.5	C
N	15	15	15	15	15	15
Base MBP	93.20±7.88	95.00±7.33	93.44±5.82	87.70±10.5	84.70±8.05	85.90±6.14
Base HR	68.30±5.12	70.80±5.36	72.90±8.70	76.80±5.60	75.30±6.69	75.6±9.47

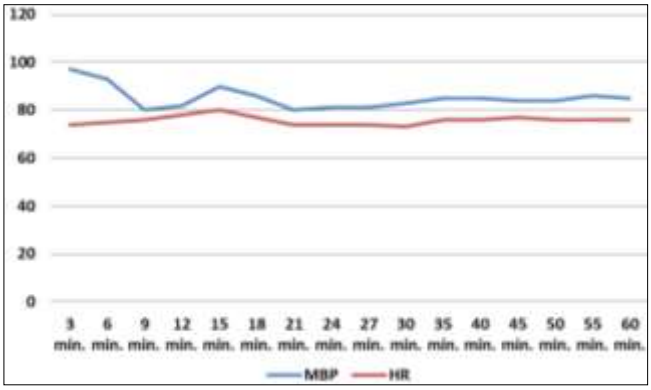
MBP = mean blood pressure (mmHg), HR = heart rate (beats/min), P-3 = phenylephrine 3mg, P-1.5 = phenylephrine 1.5mg, C = control, n = number of patients, Mean ± SD

After doing statistical analysis for testing of association between the group using X2 test it was found that episode of bradycardia requiring treatment with atropine were higher in P-3 (hypertensive and normotensive) group compared with control (hypertensive and normotensive) group ($p<0.05$) and P-1.5 (hypertensive and normotensive) group ($p<0.05$). Whereas episode of hypotension requiring treatment with ephadrin were higher in control (hypertensive and normotensive) group compared to P-3 (hypertensive and normotensive) group ($p<0.001$) and P-1.5 (hypertensive and normotensive) group ($p<0.001$). No statistically significant association in hypotensive episode were found between P-3 (hypertensive and normotensive) group and P-1.5 (hypertensive and normotensive) group ($p>0.05$) as shown in table 3. There was no statistically significant changes in heart rate over the study period in the study medication group (HP-3, HP-1.5, NP-3, NP-1.5) ($p>0.05$) found. Whereas heart rate shows significantly higher value at 12, 15 and 30 minutes and lower value at 9 and 21 minutes ($p<0.05$) as shown in table 3, graph 1.

Table 3: Results and Hemodynamic Adverse Effects after Study Medication.

Variable	Hypertensive			Normotensive		
	P-3	P-1.5	C	P-3	P-1.5	C
N	15	15	15	15	15	15
Incidence of hypotension	0	0	11 (73%)	0	1 (6.6%)	13(86%)
Incidence of bradycardia	4 (26%)	1 (6.6%)	0	3 (20%)	1 (6.6%)	0
Incidence of hypertension	0	0	0	0	0	0

Incidence of hypotension, bradycardia, and hypertension after study medication is expressed as (%), P-3 = phenylephrine 3mg, P-1.5 = phenylephrine 1.5mg, C = control, n = number of patients



Graph 1: Hemodynamic variable IN HC Group

Discussion

Our study showed significantly lower incidence of hypotension with both 3mg and 1.5mg intramuscular phenylephrine compared to the control group in both hypertensive and normotensive patients. This was in complete agreement to study performed by Ayorinde BT *et al*[7], who performed study on 108 patients undergoing elective Caesarean section under spinal anaesthesia, assigned to four groups. Group 1 received pre-emptive phenylephrine 4 mg i.m., group 2 received phenylephrine 2 mg intramuscular, group 3 received ephedrine 45 mg intramuscular, while controls received an intramuscular injection of saline, all given immediately after induction of spinal anaesthesia. They concluded that pre-emptive i.m. phenylephrine 4 mg reduce the severity of hypotension and the total dose of rescue i.v. ephedrine during spinal anaesthesia for Caesarean section. The reason for the requirement for high dose of phenylephrine in their study would have been due to requirement of higher level of block for caesarean section.

Our study is partly in agreement to study performed by Nishikawa el al. (45), who found that in normotensive groups, both doses (3mg and 1.5mg) decreased the severity of hypotension and the required dose of rescue IV ephedrine. In the hypertensive groups, 3 mg of phenylephrine decreased both the severity of hypotension and the required dose of rescue ephedrine, and 1.5 mg of phenylephrine reduced the ephedrine requirement but failed to obtund the hypotensive response. In both normotensive and hypertensive patients, 1.5 mg of phenylephrine did not cause hypertension, whereas 3 mg of phenylephrine did. One possible explanation for this result could be related to the lower level of the sensory block in our study. The incidence of hypotension during spinal anesthesia appears to be directly related to the level of sensory block [8]. Carpenter *et al*. [9] suggested that a peak block height of T5 or higher confers a threefold increase in the odds of developing hypotension. In this study, the sensory block height was T9, with a range of T8 to T10.

Intramuscular administration of 1.5 mg of phenylephrine, however, failed to attenuate the percentage reduction of mean blood pressure after spinal anesthesia in elderly patients with hypertension. In addition to the increase in sympathetic nervous system activity with aging, preexisting hypertension causes an exaggerated circulatory response to several forms of stress because of long-term persistent vascular hyper-reactivity [10]. Therefore, intramuscular administration of 1.5 mg of phenylephrine would not have a sufficiently strong effect to attenuate severe hypotension after spinal anesthesia in hypertensive patients, although its action was sufficient to maintain the hemodynamic stability after spinal anesthesia in normotensive patients. In contrast, in our study 1.5mg of phenylephrine was effective in

preventing spinal induced hypotention. The reason for this would have been a lower level of sensory block, different drug and dose used for sub-arachnoid block and different study population in our study.

As for the occurrence of adverse events in the use of phenylephrine, bradycardia after study medication occurred in 20% of the patients in the normotensive phenylepherine 3mg group and 26% of the patients in the hypertensive phenylephrine 3mg group in our study. Care should therefore be taken when administering intramuscular 3 mg of phenylephrine, especially to patients with low basal heart rate. The reason for this is believed to result from at least two causes: blockade of sympathetic cardio accelerator fibers and decreased venous return to the heart. A high level of sensory blockade by spinal anesthesia causes both of these effects. However, decrease in preload has been reported to be the main cause of large decreases in heart rate [11, 12]. Therefore, severe bradycardia can develop during spinal anesthesia even when the sensory blockade level is below to the one necessary to produce complete sympathetic blockade.

Carpenter *et al*. [9] observed that peak sensory block height causing the development of severe bradycardia was above T5; moreover, the use of phenylephrine for the treatment of spinal hypotension has been cautioned against because bradycardia can develop when the level of sensory block is above T7. In our study, in addition to the low level of sensory block, crystalloid preloading of 12 mL/kg was performed, with 8 mL/kg of the preload given before and 4 mL/kg after intrathecal injection. The low level of block, positioning of patient and the moderate fluid preloading might have been the main factors counteracting the development of bradycardia. The total number of patients in this study, however, was too small to determine the safety against bradycardia. Therefore, a large study may be needed to confirm its safety.

The timing of intramuscular injection of phenylephrine to achieve optimal efficacy is difficult to predict. The peak effect of IM injection of phenylephrine has been suggested by results of pharmacokinetic studies to be 10–15 minutes after administration[13]. However, in our study, we found reductions in the incidence of spinal anesthesia-induced hypotension in all phenylephrine groups, with no difference in the times Additionally, no hypertension was found after IM administration of phenylephrine, when a peak effect of phenylephrine would have been expected. This suggests that the IM administration of phenylephrine immediately after the induction of spinal anesthesia is not too late to achieve a beneficial effect.

Conclusion

Pre-emptive injection of intramuscular 1.5 mg of phenylephrine along with moderate fluid loading is a safe and effective method for reducing the incidence of hypotension associated with hyperbaric bupivacaine spinal anesthesia during lower limb and lower abdominal surgery, provided level of block is limited to lower thoracic segments.

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