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ORIGINAL RESEARCH

Optimal dose of phenylephrine infusion in the prevention of spinal anaesthesia-induced hypotension in elderly patients

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Background: Phenylephrine is one of the drugs of choice in the prevention of spinal anaesthesia-induced hypotension in the elderly. The optimal dose is yet to be established in elderly patients, hence this study.

Methods: This was a randomised, double-blind study on patients aged ≥ 65 years undergoing elective lower limb and urological surgeries under subarachnoid block. A total of 57 patients were randomised into groups A, B, and C and each group contained 19 patients. Group A received 50 µg/min, group B received 75 µg/min, and group C received 100 µg/min of phenylephrine infusion immediately after the induction of spinal anaesthesia. Non-invasive blood pressure and pulse rate (PR) were recorded after the commencement of phenylephrine infusion. Onset of hypotension, episodes of hypotension, reactive hypertension, and bradycardia were recorded in each group and also compared across the groups.

Results: Hypotension was prevented without any side effects of phenylephrine in group A; one patient (5.3%) in group B had an episode of hypotension at the sixth minute. The difference in the incidence of hypotension across the groups was not statistically significant ($p = 0.617$). Four patients (21.1%) in group B and nine (47.3%) in group C had reactive hypertension. The difference in the incidence of reactive hypertension among groups was statistically significant ($p = 0.002$). Bradycardia occurred in one patient (5.3%) in group B and three (15.8%) in group C. There was no statistically significant difference ($p = 0.152$) in the incidence of bradycardia across the three groups.

Conclusion: The optimal dose of phenylephrine infusion that prevented spinal anaesthesia-induced hypotension without any side effects in elderly patients was 50 µg/min.

Keywords: elderly, hypertension, hypotension, phenylephrine, spinal anaesthesia

Introduction

Elderly patients (aged ≥ 65 years) have surgery at a rate of two to three times that of younger patients.[1] Spinal anaesthesia is one of the most frequently used anaesthetic techniques in this population because many of the procedures they present with are amenable to this technique.[2] Some known advantages of spinal anaesthesia include a reduction in perioperative blood loss as well as a reduction in the incidence of deep venous thrombosis and pulmonary embolism.[3] However, hypotension is the most common complication with a reported incidence of 66% in elderly patients.[4]

The effect of hypotension is more debilitating in this age group due to decreased physiological reserve, blunted cardiac reflexes, compromised blood supply to various vital organs, and change in circulatory volume, resulting in a disposition to congestive heart failure following fluid administration.[5] Therefore, there is a need for early prevention and/or prompt treatment when hypotension occurs. Aging is associated with sympathetic nervous system deregulation, which includes cardiac and vascular beta adrenergic receptors. Beta adrenergic receptor-induced vasorelaxation declines with age. This results in age-related cardiovascular impairment.[6] Meanwhile, spinal anaesthesia causes sympatholysis leading to vasodilatation. The associated pooling of blood in the capacitance vessels ultimately results in the side effect of spinal anaesthesia-induced hypotension. These factors make hypotension more common in elderly patients.

Several strategies have been used to prevent spinal anaesthesia-induced hypotension. Among these are glycopyrrolate, colloid and crystalloid infusion, ephedrine, atropine, and ondansetron.[2,7,8,9]

Phenylephrine is a direct-acting synthetic sympathomimetic drug administered by both infusion and intermittent bolus. The side effects include bradycardia, hypertension, nausea, vomiting, headache, and dizziness.[10] A phenylephrine infusion has been shown to decrease the number of hypotensive episodes in elderly patients during orthopaedic surgeries; however, its dose-dependent side effect of bradycardia is a drawback.[11] Infusion doses of phenylephrine that have been used in literature are 50 µg/min, 75 µg/min, 100 µg/min, and 120 µg/min.[9,11,12-14] The majority of these studies were done in parturients for a caesarean section, with a paucity of studies in the elderly population. Meanwhile, the optimal dosing regimen of phenylephrine infusion is yet to be established and current practice includes both phenylephrine infusion and intermittent bolus administration.[11]

This study aimed to determine the optimal dose of phenylephrine infusion that would prevent hypotension without causing the dose-dependent side effect of bradycardia during spinal anaesthesia in the elderly.

Methods

This randomised, double-blind study was approved by the Ethics and Research Committee, and conducted between January 2020 and May 2020. The study included all consenting elderly patients (aged ≥ 65 years) of American Society of Anesthesiologists (ASA) physical status I and II who presented for either elective lower limb or urological surgeries under spinal anaesthesia. All patients who fulfilled the inclusion criteria were recruited after obtaining informed consent.

The exclusion criteria included the following: patient's refusal, patients who could not carry out instructions, uncooperative patients, body mass index (BMI) ≥ 30 kg/m^2, patients with baseline hypertension or bradycardia, and patients with contraindications to spinal anaesthesia or the administration of phenylephrine.

The sample size was determined using the formula by Kadam and Bhalerao.[15] Of the estimated sample size, 10% was added to make room for attrition, hence the total sample size was 57.

Patients enrolled on the study were randomly allocated into one of the three groups (A, B, and C) of 19 patients each using a computer-generated randomisation sequence prepared by a statistician. The randomisation was done at the theatre reception area on the morning of surgery. Allocation concealment was ensured using sequentially numbered opaque envelopes kept in a large box. Group A received 50 µg/min, group B received 75 µg/min, and group C received 100 µg/min of phenylephrine infusion. Each patient picked a sequentially numbered envelope from the box and handed it over to the theatre pharmacist who subsequently prepared the drug in a 20 ml syringe according to the allocated group inside the envelope. The drug was handed over to the anaesthetist (investigator) who performed the spinal anaesthesia. The patient and the anaesthetist were blinded to the grouping and dose of phenylephrine until the end of the study when this was disclosed by the statistician who prepared the randomisation sequence.

In the theatre, each patient was positioned in the sitting position with the back flexed. The anaesthetist scrubbed, gowned, and gloved, then prepared the patient's back with 0.5% chlorhexidine-cetrimide (Savlon®) solution and methylated spirits, thereafter covered with a fenestrated drape. The L3/L4 intervertebral space was identified using the iliac crest as a reference. A skin wheal was raised using 3 ml of 1% lignocaine. A 20 gauge introducer was placed in the intervertebral space through which a 25 gauge Whitacre (pencil point) spinal needle (Shandong Sinorgmed Co., Ltd. China) was passed, with the side hole on the spinal needle directed cephalad. Correct placement of the needle in the subarachnoid space was confirmed by the free flow of cerebrospinal fluid after withdrawal of the stylet. After this, 3 ml of 0.5% heavy bupivacaine was injected slowly through the spinal needle without barbotage. The spinal needle, together with the introducer, was removed thereafter and the site of injection was dressed with sterile gauze and adhesive tape. The patient was subsequently positioned back in the supine position. The phenylephrine infusion was commenced immediately after the institution of spinal anaesthesia using a syringe driver (Perfusor® compact, B/Braun syringe driver) for the respective groups at a rate of 1 ml/min, and continued for 10 minutes.

The patients' pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded every two minutes for the first 10 minutes, and every five minutes for the next 20 minutes when the study came to an end. There was continuous electrocardiogram (ECG) and SpO_2 monitoring throughout the study period. Monitoring of all the parameters continued every five minutes until the end of surgery. The dermatomal level of sensory block was assessed by the loss of cold sensation using an ethyl alcohol-soaked gauze pad bilaterally every three minutes for 15 minutes. Hypotension was defined as a ≥ 20% drop in MAP from baseline.[11] Hypertension was defined as a ≥ 20% increase in MAP from baseline.[11] Bradycardia was defined as a heart rate < 50/min.[11]

Patients who developed hypotension despite the administration of ongoing phenylephrine without bradycardia received an additional 100 µg of phenylephrine bolus per episode of hypotension. Patients who developed hypotension with bradycardia were to be treated with ephedrine and withdrawn from the study. Bradycardia was treated with 0.6 mg of atropine bolus. Patients who developed hypertension had the phenylephrine infusion stopped. A high spinal was to be treated by giving 100% oxygen via a face mask, placing the patient in a head-up position, and if indicated, patients were to be intubated and ventilated until the block wore off. Subsequently, the patient would be withdrawn from the study. The number of patients who had episodes of hypotension, reactive hypertension, and bradycardia in each group was recorded. Patients with high spinal, failed spinal, or incomplete block necessitating conversion to general anaesthesia (GA) were to be withdrawn from the study.

The optimal dose of phenylephrine was defined as the dose associated with the lowest incidence of hypotension and bradycardia.

Statistical analysis

IBM SPSS Statistics 20.0 (IBM, Armonk, NY, USA) was used for data analysis. Descriptive analyses of normally distributed numeric variables such as MAP and PR were carried out using their mean and standard deviations (mean ± SD). Inferential analyses were performed using the chi-square ($\chi 2$) test to compare proportions between categorical variables among patients in the study groups. Also, the one-way analysis of variance (ANOVA) was used for comparison across the study groups. The level of statistical significance was determined at $p < 0.05$.

Table I: A comparison of the patients' demographic characteristics

Profile	A (*n* = 19)	B (*n* = 19)	C (*n* = 19)	*p*-value*
Age (years)	75.91 ± 6.91	75.95 ± 6.97	73.47 ± 7.91	0.255
Weight (kg)	67.00 ± 4.66	66.21 ± 7.04	65.16 ± 8.86	0.724
Height (m)	1.61 ± 0.07	1.62 ± 0.06	1.64 ± 0.07	0.420
BMI (kg/m^2)	26.00 ± 1.76	24.84 ± 2.71	24.26 ± 2.18	0.062
Gender (5%)				
Male	13 (68.4)	15 (78.9)	14 (73.7)	0.762
Female	6 (31.6)	4 (21.1)	5 (26.3)	
ASA (%)				
I	16 (84.2)	13 (68.4)	9 (47.4)	0.055
II	3 (15.8)	6 (31.6)	10 (52.6)	

Values are in mean ± SD except for gender and ASA status
*ANOVA except for gender and ASA status that are chi-square

Results

All 57 elderly patients who were recruited and randomised into groups A, B, and C completed the study.

There was no significant difference in the demographic variables ($p > 0.05$) (Table I) and baseline haemodynamic parameters ($p > 0.05$) (Table II) across the study groups.

Table III compared the mean PR at different intervals across the groups. However, the difference in mean PR across the three groups throughout the study period did not reach statistical significance ($p > 0.05$).

In Table IV, the mean MAP values were similar across the groups in the first two minutes, with group B exhibiting higher values. These were, however, not statistically significant ($p > 0.05$). Meanwhile, there was a statistically significant difference ($p < 0.05$) in mean MAP across the three groups from the fourth minute through to the end of the study period. In group C, the mean MAP was highest from the sixth minute through to the end of the study period.

One patient (5.3%) in group B had an episode of hypotension. The patient was a female without any comorbidity and the oldest among the study population (82 years). The time to onset of hypotension was six minutes. No episode of hypotension was recorded in groups A and C, however, the difference in the

Table II: Comparison of baseline haemodynamic parameters before the induction of spinal anaesthesia

	A (*n* = 19) Mean ± SD	B (*n* = 19) Mean ± SD	C (*n* = 19) Mean ±S D	*p*-value*
PR (beats/min)	81.84 ± 5.79	80.00 ± 9.68	79.63 ± 11.64	0.739
MAP (mmHg)	72.89 ± 4.53	74.84 ± 6.08	73.84 ± 6.60	0.589
SBP (mmHg)	123.53 ± 7.37	121.31 ± 11.07	126.68 ± 8.83	0.206
DBP (mmHg)	71.84 ± 8.09	72.68 ± 10.23	75.21 ± 8.93	0.501
SpO_2	97.21 ± 0.71	97.05 ± 0.78	96.89 ± 0.99	0.513

*ANOVA

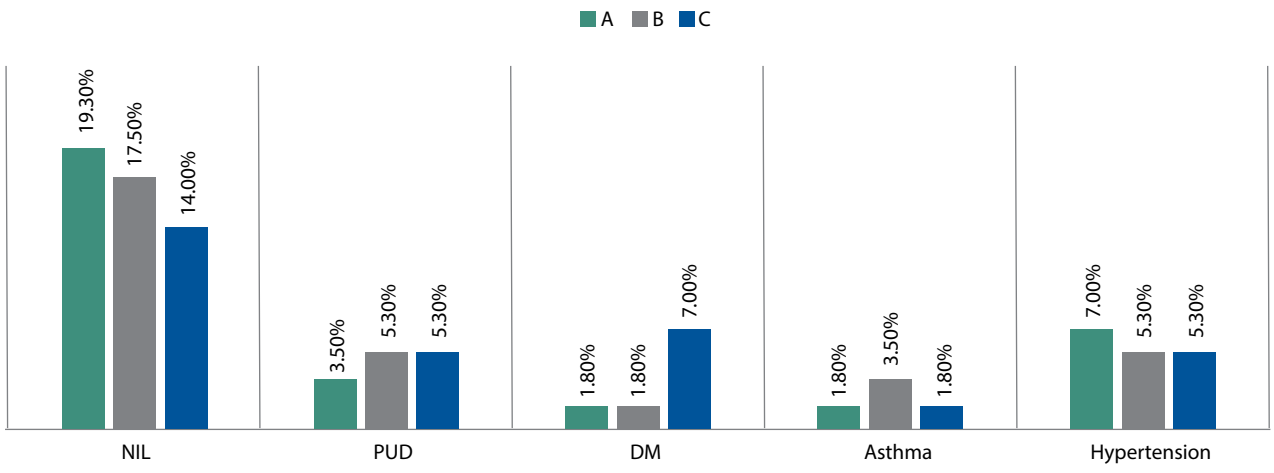

Figure 1: Comparison of the occurrence of comorbidities across the study groups ($p = 0.816$)
PUD – peptic ulcer disease; DM – diabetes mellitus

Table III: Comparison of mean PR (beats/min) at different time intervals across the groups

	A	B	C	*p*-value*
	Mean + SD	Mean + SD	Mean + SD	
PR_0	81.74 + 5.72	80.00 + 9.68	79.95 + 12.04	0.805
PR_2	84.32 + 6.23	81.68 + 9.34	82.53 + 12.30	0.692
PR_4	83.74 + 6.24	77.68 + 9.82	80.37 + 11.12	0.142
PR_6	79.26 + 7.57	73.63 + 9.40	74.84 + 10.79	0.158
PR_8	75.68 + 7.71	71.74 + 9.20	70.89 + 13.26	0.320
PR_{10}	74.53 + 7.09	70.68 + 9.20	69.79 + 10.33	0.234
PR_{15}	73.89 + 6.59	71.53 + 7.40	71.26 + 7.23	0.457
PR_{20}	73.89 + 5.83	72.47 + 6.92	73.32 + 6.96	0.801
PR_{25}	74.95 + 6.15	72.26 + 6.84	75.26 + 6.43	0.301
PR_{30}	75.00 + 4.52	71.58 + 6.66	74.11 + 6.32	0.190

*ANOVA

Table IV: Comparison of MAP (mmHg) at different time intervals across the groups

MAP	A	B	C	*p*-value
	Mean + SD	Mean + SD	Mean + SD	
MAP_0	72.42 + 4.69	74.53 + 5.61	73.84 + 6.60	0.512
MAP_2	71.42 + 5.70	75.37 + 4.63	73.16 + 6.58	0.111
MAP_4	71.74 + 6.27	77.63 + 4.84	76.32 + 8.13	0.020*
MAP_6	73.11 + 6.08	79.68 + 5.50	81.89 + 10.26	0.002*
MAP_8	74.32 + 5.29	83.21 + 8.63	86.74 + 11.33	0.000*
MAP_{10}	75.53 + 5.25	84.26 + 10.62	87.16 + 8.87	0.000*
MAP_{15}	76.00 + 4.30	83.58 + 8.95	84.63 + 8.06	0.001*
MAP_{20}	76.58 + 4.64	82.89 + 10.81	84.16 + 8.07	0.014*
MAP_{25}	76.32 + 4.19	81.58 + 7.59	83.32 + 7.40	0.005*
MAP_{30}	75.79 + 3.93	81.47 + 7.82	83.37 + 6.77	0.002*

*$p < 0.05$ is considered statistically significant (ANOVA)

incidence of hypotension among the groups was not statistically significant ($p = 0.617$).

No patient had any episode of bradycardia in group A, one patient (5.3%) had in group B, while three patients (15.8%) had bradycardia in group C. All patients who had bradycardia experienced only one episode each. The differences in the incidence of bradycardia across the three groups did not reach a statistically significant level ($p = 0.152$).

No episode of reactive hypertension was observed in group A. Four patients (21.1%) in group B and nine patients (47.3%) in group C had episodes of reactive hypertension. The difference in the incidence of hypertension among the groups was statistically significant ($p = 0.002$).

A comparison of the occurrence of comorbidities across the study groups is presented in Figure 1. The majority of patients (50.8%) had no comorbidities. Hypertension was the most prevalent comorbidity (17.5%), while bronchial asthma had the lowest prevalence (7.0%) among the study groups. There was no statistically significant difference in the distribution and prevalence of comorbidities across the study groups ($p = 0.816$).

Discussion

This study has shown that the three doses of phenylephrine infusion in elderly patients undergoing orthopaedic and urological surgeries under spinal anaesthesia were all effective in preventing spinal anaesthesia-induced hypotension. However, only a dose of 50 µg/min was found to prevent hypotension without causing any of the known side effects of phenylephrine.

Abbasivash et al.[16] observed an 8.7% incidence of hypotension and a 13% incidence of bradycardia in adult patients who received a prophylactic 50 µg phenylephrine bolus during spinal anaesthesia for hip surgery. This finding is at variance with our study where a 50 µg/min phenylephrine infusion was administered. The better control of hypotension in the index study may be due to the use of an infusion regimen rather than bolus administration. More so, the effectiveness of the phenylephrine infusion in the index study may be due to its prophylactic rather than therapeutic use. This is supported in the study by das Neves et al.[17] who observed that a prophylactic continuous infusion, rather than a therapeutic phenylephrine bolus dose, is more effective in reducing the incidence of hypotension.

Žunić et al.[18] prophylactically infused 250 µg of phenylephrine, over 30 minutes (≈ 8 µg/min), after a subarachnoid injection of 15 mg of levobupivacaine at L2/L3 during spinal anaesthesia in elderly orthopaedic patients with an associated 14.2% incidence of hypotension. Conversely, the 50 µg/min of phenylephrine infusion in the index study was not associated with any incidence of hypotension. The level of injection at L2/L3 may be responsible for the conflicting results among the compared studies since there is a possibility of more cephalad spread at a higher injection site compared to a lower injection site.

The time to onset of the only incidence of hypotension in group B (75 µg/min group) was six minutes. This was in contrast with the work of Ferré et al.[11] in which the time to onset of hypotension after infusing 100 µg/min of phenylephrine in their subjects was longer (15 minutes). This difference in the time to onset of hypotension might have resulted from the higher dose of phenylephrine (100 µg/min) that was associated with hypotension in the study, as opposed to the lower dose of phenylephrine (75 µg/min) that was associated with hypotension in the index study. From the aforementioned study, it can be said that the time to onset of hypotension depends on many factors that include the age of the patient, dose of phenylephrine, mode of administration of phenylephrine (bolus vs. infusion), and methodologies employed in the studies cited.

In our study, no incidence of hypotension was associated with the use of 100 µg/min of phenylephrine infusion; however, 15.8% of patients had bradycardia and 47.3% had reactive hypertension in the groups. Meanwhile, in a similar study, Mostafa et al.[19] observed no incidence of hypotension in their study group (100 µg/min of phenylephrine infusion). In contrast to the index study, they observed bradycardia in 36% of patients as well as reactive hypertension in 36% of patients in their study

groups respectively. In our study, bradycardia following the administration of phenylephrine infusion is dose-dependent. This finding is in agreement with the result of a previous study.[12]

In their study on the comparison of spinal anaesthesia-induced fall in blood pressure in normotensive and hypertensive patients, Yousaf et al.[20] confirmed that the spinal anaesthesia-induced fall in blood pressure was greater in hypertensive, elderly male patients than in normotensive patients. This is tangential to the findings of the index study in which the hypotensive patient was a female, had no comorbidity, and was the oldest among the three study groups. Singla et al.[21] observed that age and females were independently associated with the development of early hypotension during spinal anaesthesia, as observed in this index study.

Poorly treated or untreated hypertension usually leads to progressive end-organ damage. In the course of practice, anaesthetists are often confronted with the fact that the complications of hypertension are themselves independent risk factors for perioperative complications.[22] Thus, 21.1% of patients in group B (75 µg/min) and 47.3% of patients in group C (100 µg/min) who developed reactive hypertension had the phenylephrine infusion stopped as part of the study procedure to forestall any deleterious effect on the patients.

Kokulu et al.[23] observed that hypotension was more frequent in patients over the age of 80 years in a study investigating the frequency of hypotension and changes in cardiac output related to spinal anaesthesia among geriatric patients. This finding is in agreement with our study, where the only case of hypotension occurred in the oldest subject among the groups, aged 82 years. Similar to the findings in our study, Malima et al.[24] observed that females are associated with a higher risk for developing spinal hypotension in a study evaluating the pre-spinal risk factors for hypotension associated with spinal anaesthesia in elderly surgical patients.

Conclusion

This study has shown that a phenylephrine infusion at a dose of 50 µg/min prevented spinal anaesthesia-induced hypotension in elderly patients without causing any of the known side effects of phenylephrine. It was observed that higher doses (75 µg/min and 100 µg/min) of phenylephrine infusion were associated with bradycardia and reactive hypertension. It can thus be concluded that 50 µg/min of phenylephrine infusion is the optimal dose for the prevention of spinal anaesthesia-induced hypotension in elderly patients.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was obtained from the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife (ERC/2018/11/04).

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