Orginal Article

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Comparison of the Effects of Intravenous Phenylephrine and Ephedrine in Treatment of Hypotension after Spinal Anesthesia in Orthopedic Surgery

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ABSTRACT

BACKGROUND AND OBJECTIVE: Hypotension after spinal anesthesia is a common and potentially dangerous complication, prompt and accurate prevention and treatment of which are of paramount importance. In the recent studies there have been conflicting results regarding the efficacy of phenylephrine and ephedrine in the prevention and treatment of hypotension after spinal anesthesia. Thus, in this study, we purport to compare the effects of phenylephrine and ephedrine in the treatment of hypotension after spinal anesthesia for lower limb orthopedic surgery.

METHODS: This double-blind clinical trial was conducted on 110 ASAI-II patients aged 40-65 years, who were candidates for orthopedic surgery of lower limbs under spinal anesthesia with 3 mL of bupivacaine 0.5%. The subjects were randomly divided into two groups of 55. After observing 20% fall in blood pressure or blood pressure less than 90/60 mm/Hg, the first group received 50 µg of phenylephrine and the second group was administered 5 mg of intravenous ephedrine. Information concerning the hemodynamic status of the patients was collected and compared.

FINDINGS: Phenylephrine was more effective in the treatment of systolic and diastolic hypotension following spinal anesthesia compared to ephedrine (systolic blood pressure: 119±10.6 vs. 112.35±10.34 nc and diastolic blood pressure: 73.42±6.67 vs. 70.05±6.15 nc). However, it should be noted that except for 2 and 4 minutes after administration of vasopressor, there was no statistically significant difference between the two groups. In both groups, heart rate elevated simultaneously with decrease in blood pressure.

CONCLUSION: The results revealed that phenylephrine was more effective in the treatment of hypotension following spinal anesthesia compared to ephedrine in lower limb orthopedic surgery.

KEY WORDS: *Phenylephrine, Ephedrine, Spinal anesthesia, Hypotension, Bupivacaine*.

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Introduction

Spinal anesthesia is commonly applied for orthopedic surgery of the lower limbs, and hypotension is a prevalent adverse effect; this complication affecting about a third of patients receiving spinal anesthesia is caused by decreased cardiac output (1). Ephedrine is a non-catecholamine and sympathomimetic agent stimulating both alpha and beta adrenergic receptors and imposes its effect through the release of norepinephrine from the autonomic nervous terminals. Although its higher efficacy than other vasopressor agents has not been established, it is considered as the treatment of choice for the treatment of hypotension after spinal anesthesia, especially for cesarean section. However, due to its potential complications such as supraventricular tachycardia, tachyphylaxis, and fetal acidosis (in caesarean section), its application has been undermined (2-6). Phenylephrine is an agonist of alpha-1adrenergic receptors, which causes vasoconstriction in a dose-dependent manner and is more effective on veins than arteries; it also enhances venous return after sympathetic block (7, 8).

Peripheral circulatory disorders in susceptible individuals, brachycardia, and fetal acidosis in pregnant women (to a lesser extent than ephedrine) are some of the adverse effects of phenylephrine (9, 10). Despite the positive effects of phenylephrine in the treatment of hypotension following spinal anesthesia, in recent studies, there is no consensus on drug selectivity (11, 12). The main cause of hypotension following spinal anesthesia is sympathetic block and there are different methods for its treatment including slight lowering of patients' head, intravenous fluids injection before blocking, and administration of sympathomimetic drugs such as ephedrine and phenylephrine (13). Despite the use of these two agents, there is a scarcity of studies on these drugs in cases of hypotension following spinal anesthesia in orthopedic surgery. Thus, in this double blind clinical trial, we aimed to compare the effectiveness of these two drugs.

Methods

This clinical trial was carried out on 110 ASAI-II patients aged 40-65 years, who were candidates for orthopedic surgery. To prevent the impact of confounding factors and homogenize the subjects, we solely studied patients undergoing lower limb orthopedic surgery. Some samples were excluded due to sensitivity to vasopressors or local anesthetics and systemic diseases such as cardiovascular, hepatic, or renal diseases. After obtaining informed consent from the participants and approval of Ethics committee of Deputy of Research (code no.: 391 127 and IRCT: 2015070920588 N3), all the patients underwent surgery after spinal anesthesia. The subjects were selected randomly through computer and patients were divided into two groups of 55. After transferring the patients to operating room, patient characteristics including age, gender, and physical condition were recorded and systolic and diastolic blood pressure and mean arterial blood pressure were considered as the standard basis for the comparison.

After transferring the patient to operating table, blood pressure and cardiovascular monitoring were carried out, and through pulse oximetry, arterial blood oxygen saturation was evaluated; all the measured variables were recorded as basis. Then, in case of no contraindications, using needle No. 24, spinal anesthesia was performed in L3- L4 and L4-L5 spinal levels in the midline and in sitting position, and 15 mg (3 mL) of bupivacaine 0.5% was injected inside the subarachnoid space, and after situating the patient in prone position, all the variables were measured and recorded every 5 minutes. In cases with more than 20% fall in systolic blood pressure, 50 µg of phenylephrine was injected to the first group and the second group was administrated 5 mg of ephedrine intravenously. If hypotension was not managed, 5 mg of ephedrine was repeated until reaching an acceptable level of blood pressure. In patients suffering from bradycardia in addition to hypotension (heart rate less than 60 bpm), intravenous atropine was administered at a dose of 0.5 mg. The required data, including systolic and diastolic blood pressure and heart rate, were recorded at 2, 4, 6, 8, 10, 20, and 30 minutes. Moreover, arterial oxygen saturation, administration of supplementary treatment, ephedrine bolus, and atropine, and side effects of ephedrine and phenylephrine were recorded in a checklist. Patients requiring changing the anesthesia method during surgery or those who needed high volumes of crystalloids (more than 3 lit) for maintenance of normal blood pressure (greater than 110/60 mm/Hg) were excluded from the study. At the end time of anesthesia, patients were transferred to the recovery room, and at arrival, they were evaluated in terms of hemodynamic status by one of the researchers.

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Repeated measures ANOVA, t-test (to compare two independent quantitative groups), and Chi-squared (for qualitative data) tests were performed using SPSS, version 20. P-value less than 0.05 was considered statistically significant.

Results

In this study, we compared patients receiving phenylephrine and ephedrine (n=55 for each group). The mean ages of the ephedrine and phenylephrine groups were 38.10±4.86 and 39.5±0.48 years, respectively, no significant difference was observed between the two groups. In terms of gender, the groups were not significantly different.

The highest level of spinal anesthesia in both groups was L5 (L3-L5). No significant differences were observed between the two groups in terms of baseline systolic blood pressure, mean arterial pressure, and diastolic blood pressure (table 1).

Table 1. Variations of systolic blood pressure, diastolic blood pressure, and heart rate in patients receiving phenylephrine and ephedrine to control hypotension following spinal anesthesia for orthopedic surgery

Group / Time	Systolic blood pressure (mm/Hg) Mean±SD			Diastolic blood pressure (mm/Hg) Mean±SD			Heart rate Mean±SD		
	Ephedrine	Phenylephrine	P	Ephedrine	Phenylephrine	P	Ephedrine	Phenylephrine	P
Before spinal anesthesia	11.2±125	9.7±125.5	0.9	7±72.4	6.2±74	0.14	19±99	17±101	0.64
At the time of vasopressor administration	7.4±92	6.8±94.9	0.71	4±58.3	5.3±57.9	0.05	17±110	16±115	0.09
2 min after administration	10±106	14±115.5	0.004	7.2±68	8.4±74	0.032	20±113.5	16±89.7	<0.001
4 min after administration	13.7±106.2	16±119	0.003	7±68	9±74	0.04	24±110	18±78.8	<00.1
6 min after administration	10±110.8	12.4±119.1	0.007	7±68.4	6.8±74	0.049	25±103.5	17±92.7	0.002
8 min after administration	8.6±113.5	10.5±120	0.21	5±71	7.2±74.4	0.13	22±104.1	16±96.1	0.11
10 min after administration	9.2±118.3	9±119.2	0.64	6±72	7±74	0.11	19±104.5	17±96.4	0.1
14 min after administration	9.5±113.5	8±119.2	0.82	5±70	5±71	0.88	15±106.4	14±97.3	0.12
20 min after administration	12±114	8±119	0.78	6±70	5±72	0.45	16±106.8	14±99.6	0.08
30 min after administration	5.5±10.117	121±7	0.6	73±6	74±5	0.6	5±14.104	7±14.99	0.9
P-value	0.024			0.029			0.01		

Within 2-6 minutes, patients receiving phenylephrine showed higher means of systolic and diastolic blood pressure and lower heart rate compared to patients receiving ephedrine; in addition, systolic pressure was significantly different at the eighth minute between two groups.

In relation to the treatment of systolic blood pressure, phenylephrine was clinically more effective, but there was no statistically significant difference between the two groups except for 2-8 minutes after administration of vasopressor (fig 1, 2, 3). Total dose of vasoconstrictor in the ephedrine group was 12.4 mg, while it was 184.4 µg in the phenylephrine group. Overall, nausea and vomiting were experienced by 15 patients in the ephedrine group and 12 subjects in the phenylephrine group, and there was no significant difference in this respect between the two groups. Side effects of phenylephrine and ephedrine were not observed in any of the patients, and cardiac arrhythmia did not occur in any of the participants.

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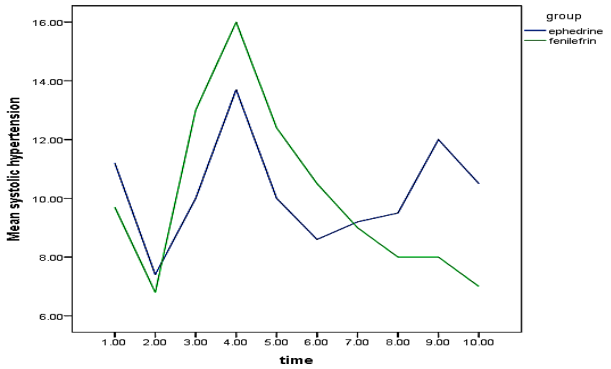

Figure 1. Changes of mean systolic hypertension over different time periods of drug administration (separately for the two groups of patients receiving ephedrine or phenylephrine)

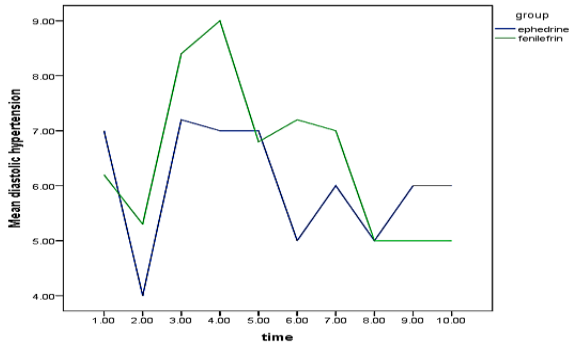

Figure 2. Changes of mean diastolic hypertension over different time periods of drug administration (separately for the two groups of patients receiving ephedrine or phenylephrine)

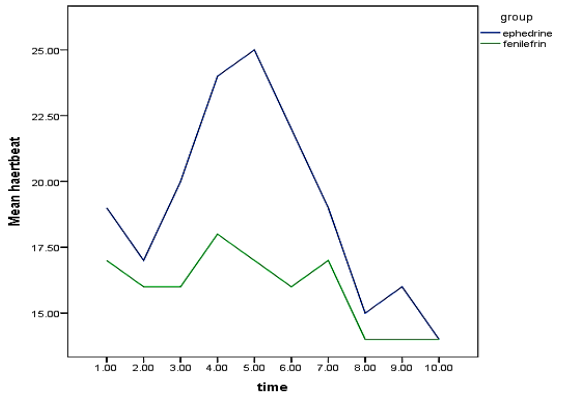

Figure 3. Changes of mean heart rate over different time periods of drug administration (separately for the two groups of patients receiving ephedrine or phenylephrine)

Discussion

Administration of phenylephrine was more effective than ephedrine in the treatment of hypotension following spinal anesthesia for lower limb orthopedic surgery. Ample studies have been performed on the methods and time of prevention and treatment of hypotension following spinal surgery; however, there is no consensus on this issue (2, 5, 14). Nonetheless, it is unanimously believed that since multiple factors are at play in the occurrence of hypotension, its treatment should include a combination of methods, and vascular fluid therapy and application of vasoconstrictors are always recommended (15). In various studies, onset of hypotension is assumed to be 5-20 minutes following spinal anesthesia depending on the type of anesthesics and patient characteristics, but most scholars emphasize on 15 to 20 minutes following spinal anesthesia, at which time, the anesthesiologist must provide special care for patient (16).

Ephedrine is a vasoconstrictor applied after spinal anesthesia, which imposes its effects through stimulation of both alpha- and beta- adrenergic receptors, and it is beneficial in patients with hypotension due to sympathetic block (e.g., hypotension after spinal anesthesia), but in the recent studies, the position of ephedrine has been undermined due to its side effects such as tachycardia, supraventricular, tachyphylaxis, and fetal acidosis (in cesarean section) (2, 8). In cases where hypotension is caused by vasodilation and sympathetic stimulation is risky for the patient (e.g., ischemic heart disease), alpha-adrenergic drugs such as phenylephrine are more suitable (2, 8, 17).

Recent studies have proved the positive effects of phenylephrine and some of them considered it as the treatment of choice after occurrence of hypotension following spinal anesthesia (6, 14, 18, 19). Nevertheless, its side effects such as bradycardia reaction, fetal acidosis (in cesarean section), and impaired peripheral blood flow should be considered (9, 14, 20, 21). Some researchers have employed combination of phenylephrine and ephedrine, but they have concluded that it had no advantages over phenylephrine alone (22). In addition, in another study by Loughrey et al., it was concluded that the combination of the two vasopressors was not more effective than ephedrine alone (4).

In the present study, the immediate impact of phenylephrine on blood pressure could be due to the shorter duration of its maximum effect (1 min) compared with ephedrine (2-5 min). Herein, we did not use vasopressors to prevent hypotension after anesthesia on account of two reasons. Firstly, it is morally wrong as we could not administer ephedrine to patients with tachycardia; secondly, clinical studies did

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not recommend vasopressors for prevention of hypotension following spinal anesthesia (2, 5, 23). In the current study, intravenous vasopressors were administrated in case of more than 20% decrease in systolic blood pressure. A total of 15 patients in the ephedrine and 12 patients in the phenylephrine groups experienced nausea and vomiting. Nausea and vomiting can be associated with the severity of hypotension, which was similar in both groups. As the duration of vasopressor response to medication decreases the incidence rate of postoperative nausea and vomiting increases (24); there was no statistically significant difference in this study. Bolus phenylephrine (50 µg) and ephedrine (5 mg) were used in this study, which is consistent with other studies. For instance, Saravanan et al. employed 100 µg of phenylephrine and 10 mg of ephedrine for this purpose (21). On the other hand, Prakash et al. assessed the effect of combination of 100 µg of phenylephrine and 6 mg of ephedrine to control hypotension following spinal anesthesia (25).

Although there have been some discussions on the methods of hypotension management and intramuscular and subcutaneous methods were recommended by some scholars, most researchers prefer its intravenous administration (26).

In our study, phenylephrine was effective in the treatment of hypotension, which is consistent with other studies (12, 14). Ephedrine also improved blood pressure, but its effect was not similar to phenylephrine, which is in line with the findings of former studies (27). Ephedrine was more effective on heart rate; some studies have shown that phenylephrine may also cause delayed increase in heart rate (11, 28-30). It seems that lower effect of phenylephrine on heart rate after spinal anesthesia might be due to lower doses of vasopressor medications applied in our study compared to some others. Another reason might be the established effect of phenylephrine as a pure agonist of alpha-adrenergic receptors, which can cause reflex bradycardia.

Our results demonstrated that phenylephrine at a dose of 50 µg and 5 mg of ephedrine for the treatment of hypotension after spinal anesthesia are appropriate, but at times close to administration, the effect of phenylephrine was statistically more significant.

The findings of this study showed that both drugs can be used for the treatment of hypotension following spinal anesthesia in patients undergoing orthopedic surgery of the lower limbs, and it should be noted that ephedrine is more suitable than phenylephrine for the treatment of bradycardia after the initial increase in heart rate following hypotension.

Limitations of the study

The results of our study cannot be generalized to people aged over 65 or under 40 years or ASA≥ 3 patients with systemic diseases. Considering our sample size and the presence of confounding factors, it seems that new findings would be achieved through expanding the sample size and considering other exclusion criteria.

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