Original Article

Comparing prophylactic effect of phenylephrine and ephedrine on hypotension during spinal anesthesia for hip fracture surgery

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Abstract

Background: Spinal anesthesia is an accepted technique in hip fracture surgery and prevention of this complication by sympathomimetic agents is of potential clinical significance. The aim of this study is to compare the effect of prophylactic phenylephrine versus ephedrine in the prevention of hypotension during spinal anesthesia in hip fracture surgery.

Materials and Methods: Ninety-two patients undergoing hip fracture surgery with the American Society of Anesthesiologists I and II were randomized to receive prophylaxis with ephedrine or phenylephrine immediately before the spinal anesthesia. Patients in the ephedrine group received an intravenous (IV) bolus of 10 mg ephedrine, and patients in the phenylephrine group received an IV bolus of 50 μg phenylephrine. We recorded mean arterial pressure (MAP), systolic and diastolic blood pressure, heart rate every 3 min in the first 10 min and then every 5 min until 30 min after spinal anesthesia, nausea and vomiting, additional vasopressor, and atropine administration.

Results: The frequency of hypotension was significantly lower in MAP, systolic and diastolic pressure in group phenylephrine in 3, 6, and 9 min after spinal anesthesia ($P = 0.002$, $P = 0.001$). There were no significant differences between two groups in heart rate at different time of study. In the phenylephrine group, lower additional vasopressor was used (8.7% and 23.9%) ($P = 0.04$). There were no significant differences between two groups in the use of atropine ($P = 0.24$), nausea and vomiting.

Conclusion: At the doses of ephedrine and phenylephrine administered in this trial, phenylephrine was better to prevent hypotension during hip fracture surgery with spinal anesthesia. Higher frequency of hypotension was observed in the ephedrine group.

Key Words: Ephedrine, hip fracture, hypotension, phenylephrine, spinal anesthesia

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INTRODUCTION

Hip fracture is more prevalent in older people. The patients have usually other underlying problems in addition to fracture. The rate of mortality among them is 14% to 36% in the first year after the fracture.[1] Studies have shown that underlying diseases can

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increase the rate of mortality in these patients.[2] In a study, it was indicated that dealing with underlying problems and possibly trying to improve them can decline the rate of morbidity from 29% to 2.9%.[3]

No special anesthesia has so far been definitely recommended for these patients and the selection of general, spinal, or epidural anesthesia may be different based on the clinical situation of the patient.[4-6] Although general anesthesia is simple and more convenient, it cannot provide thrombolytic property which is created through local anesthesia, i.e., spinal or epidural anesthesia for the patients. Spinal anesthesia alone or when added to a general anesthetic decreases postoperative hypercoagulability, decreasing the risk of thromboembolism.[4] Another advantage of regional anesthesia is less bleeding during surgery in orthopedic patients. From 1966 on, 17 studies have been conducted in this field which have shown that in regional anesthesia, blood transfusion is needed less during surgery compared to general anesthesia in hip arthroplasty surgery.[7] Using bupivacaine 0.5%, spinal anesthesia can provide appropriate regional anesthesia for patients with hip fracture.[8] Cardiovascular effects of neuraxial block are similar to the intravenous (IV) use of alpha 1 and beta blockers and their effects on the cardiovascular system which can be emerged as decline in heart rate and arterial blood pressure.[9] In old patients and those who suffer from heart diseases, the rate of peripheral vascular resistance after spinal anesthesia may be reduced up to 25%, and the amount of cardiac output may drop to 10% as well.[10] Ephedrine is a noncatecholamines sympathomimetic drug, which is usually used IV. Ephedrine increases blood pressure and heart rate.[11] Phenylephrine is an alpha-1 receptors agonist that is used when peripheral vasoconstriction is needed and heart records are acceptable and appropriate similar to what occurs in spinal anesthesia. The cardiovascular effects of neuraxial blocks are similar in some ways to the combined use of IV alpha 1- and beta-adrenergic blockers: Decreased heart rate and arterial blood pressure. When phenylephrine is IV used, it is a drug with rapid onset and short duration of action (5–10 min).[12] In previous studies, the effect of phenylephrine and ephedrine has been used to prevent hypotension in spinal anesthesia and different results have been taken. Magalhães *et al*. in 2009 compared the efficacy of ephedrine and phenylephrine in the prevention and treatment of maternal hypotension during spinal block. Two groups to receive IV prophylactic ephedrine (Group E, $n = 30$, dose = 10 mg) or phenylephrine (Group P, $n = 30$, dose = 80 μg). They found that ephedrine was more effective than phenylephrine in the prevention of hypotension.[13] Nishikawa *et al*. in 2002 investigated prophylactic intra muscular small dose phenylephrine on spinal anesthesia-induced hypotensive during surgical repair of hip fracture in the elderly.[14] In this study, the effect of preventive single-doses of IV phenylephrine and ephedrine has been examined to prevent hypotension after spinal anesthesia for hip fracture surgery in the operating room (C) at Imam Khomeini Hospital in Urmia University of Medical Sciences, Urmia, Iran.

MATERIALS AND METHODS

This is a randomized double-blind clinical trial study performed on 92 patients aged between 40 and 70 years old, American Society of Anesthesiologists (ASA) class one and two under hip fracture surgery with spinal anesthesia after it was confirmed by the Research and Ethics Committee and informed consent was taken from the subjects. On the basis of the formula for the comparison of two ratios, and the ratio of pressure loss Groups E and *P* were 70% and 93.3%, respectively,[14] the significance level of 5%, power of 80%, equal sample size in each group, 46 patients were assessed in each group [Figure 1]. The sample size was calculated using software STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) and comparing two ratios. Patient with any conditions in which spinal anesthesia had been contraindicated for them and a history of allergies to medications were excluded from the study. In the operating room, patients were initially monitored by noninvasive blood pressure, electrocardiogram, and pulse oximetry. All patients received ringer serum 5 to 7 ml/kg before any intervention. Spinal anesthesia was performed with a 25-gauge Quincke bevel needle (EXEL) through L2–L3 or L3–L4 interspaces vertebral in a way that the fractured side is located in the upper part and 12.5 mg of hyperbaric bupivacaine 0.5% was injected after securing the subarachnoid space and that the patients were located in the supine position. Syringes containing ephedrine and phenylephrine were already prepared and labelled by someone else in the way that 46 syringes contained ephedrine and 46 others phenylephrine. A syringe with any label was randomly taken out from the box and injected to the patients such that the researcher was informed of the issue after he filled in the whole questionnaires. Ephedrine and phenylephrine were prepared as syringes 5 cc containing 5 ml solutions of distilled water. Ephedrine (Sterop Company, Belgium) syringes contained 10 mg per cc and phenylephrine (Aboreyhan Company, Iran) 50 μg/cc and immediately before spinal anesthesia, one cc of each was randomly injected IV. Oxygen was used for patients as 4–6 L/min via a face mask. Blood pressure was measured and recorded every 3 min in the first 10 min and then every 5 min

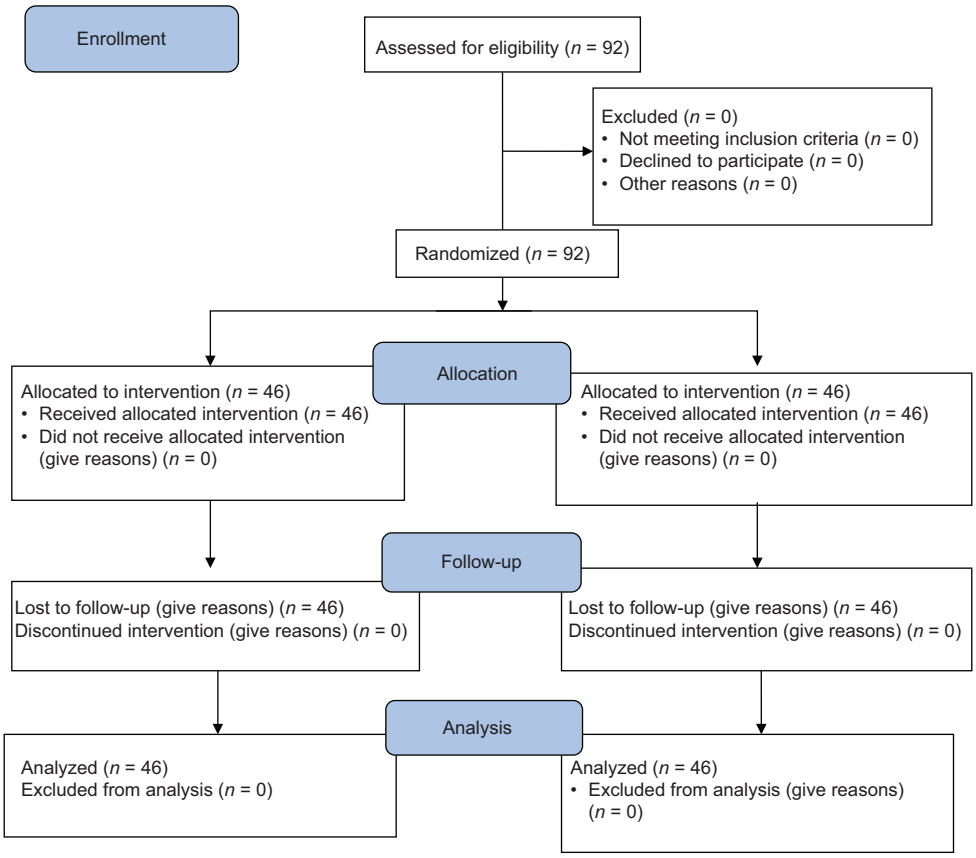

Figure 1: Study CONSORT flow diagram

until 30 min after spinal anesthesia and if a decrease in systolic blood pressure to 80% of baseline happened, the rate of infusion serum was increased and 50% of the initial dose of vasopressor was used. The decline in heart rate was treated by atropine 0.75 mg. The average change in mean blood pressure, systolic and diastolic blood pressure, heart rate, and the frequency of nausea (discomfort before vomiting. Yes or no) and vomiting (push out stomach contents from the mouth with pressure) were measured and recorded during the surgery. The rate of vasopressor and atropine needed was recorded in each group. The data were recorded in some prepared forms and were statistically analyzed by *t*-test and Fisher exact test using SPSS 18 software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

In this randomized, double-blind clinical trial study, 92 patients aged between 40 and 70 years old, ASA class one and two who were under hip fracture surgery by spinal anesthesia were examined in two groups of patients receiving ephedrine as the control group and phenylephrine as the experimental group. The mean age of patients was 51.54 ± 13.41 years in the experimental group and 52.34 ± 12.47 years in the control group. The mean body mass index (BMI) was 24.23 ± 2.43 kg/m^2 in the experimental group and 25.36 ± 2.20 kg/m^2 in the control group. According to *t*-test, there was no statistically significant difference between the two groups in terms of age and BMI [Table 1].

In terms of the basis (*t*-test) average mean blood pressure, i.e., before spinal anesthesia, there was no statistically significant difference between the groups, while the decline in average blood pressure was more in the group receiving ephedrine than the group receiving phenylephrine in 3, 6, and 9 min after spinal anesthesia which was statistically significant. In other time points, there was no statistically significant difference between the two groups [Table 2].

The basis (*t*-test) mean systolic and diastolic blood pressure, i.e., before spinal anesthesia was measured and there was no statistically significant difference between the two groups, whereas the mean systolic and diastolic blood pressure was lower in the group receiving ephedrine than the group receiving phenylephrine in 3, 6, and 9 min after spinal anesthesia. In this regard, the difference was statistically significant too (P = 0.01). There was no statistically significant difference for the rest of the

time between the two groups. The average heart rate did not differ at baseline and the following measured minutes between the two groups [Table 3].

Among the subjects, four patients (8.7%) and three cases (6.5%) had nausea during surgery out of 46 patients receiving ephedrine and phenylephrine. Based on Fisher exact test, there was no statistically significant difference between the two groups in the frequency of nausea during surgery ($P = 0.5$). Vomiting was observed in none of the patients participating in the study during the operation.

Out of 46 patients receiving phenylephrine four patients (8.7%) required the repletion of vasoconstrictor as well as 11 cases (23.9%) in the group receiving ephedrine with a statistically significant difference ($P = 0.04$). Out of 46 patients in the group receiving phenylephrine, six patients (13%) and three cases (6.5%) from the group receiving ephedrine received atropine that there was no statistically significant difference between the two studied groups in the dose of atropine ($P = 0.24$) [Table 4].

Table 1: Comparison mean of age and body mass index in the two groups

Variables	Group	Mean±SD	*P*
Age (years)	Ephedrine	51.54±13.41	0.76
	Phenylephrine	52.34±12.47	
BMI (kg/m^2)	Ephedrine	24.25±2.43	0.61
	Phenylephrine	25.36±2.2	

BMI: Body mass index, SD: Standard deviation, and used of independent sample *t* test

Table 2: Comparison of average mean blood pressure (mmHg) in the times measured between the two studied groups

Time (min)	Ephedrine	Phenylephrine	*P*
Basis	86.17±6.10	88.27±6.93	0.12
3	79.08±8.80	84.69±7.55	0.002*
6	75.28±8.31	82.05±6.32	0.001*
9	73.26±7.89	80.48±7.44	0.001*
15	86.69±7.55	87±9.23	0.19
20	85.05±5.65	87.11±5.57	0.08
25	89.89±6.69	90.87±5.22	0.43
30	88.88±7.83	89.81±6.44	0.52

Data shown Mean±Standard deviation, and used of independent sample *t* test

DISCUSSION

During and after surgery, mortality is affected by the method of anesthesia and surgery. Pathophysiological changes associated with age, comorbidities, and treatment with various drugs make old people more sensitive to drugs used in general anesthesia for surgery. Spinal anesthesia is often used for fracture surgery as a result of trauma hip in elderly people whose most common side effect is hypotension. Hypotension is more prevalent in older people in this method.[14] In this study, the preventive effect of IV ephedrine and phenylephrine was compared with each other to prevent spinal anesthesia-induced hypotension. It seems that the entire injection of IV fluid cannot prevent hypotension following the sympathectomy of spinal anesthesia and this effect can create diverse effects on old patients, especially those who have cardiovascular problems.[15] In this study, the decline in average mean blood pressure was lower in the group receiving IV phenylephrine compared to that in ephedrine in 3, 6, and 9 min and this difference was statistically significant. Similarly, additional vasopressor dose was used for the group receiving ephedrine to prevent hypotension. This difference was statistically significant too. In the group with the IV infusion of phenylephrine, the number of patients receiving atropine to treat bradycardia was higher compared to that to ephedrine. However, this difference was not statistically significant. Currently, vasoconstrictor is an alternative for the treatment of hypotension from ephedrine spinal anesthesia while it seems that the influence of the drug is not suitable for increasing heart rate by stimulating the beta receptors for an older person, especially with a history of heart disease and causes heart complications.[16] So, phenylephrine which has not such side effect can be a suitable alternative for these patients. In 2002, Husseini *et al*. compared the effect of mucosal phenylephrine and IV ephedrine on the prevention of hypotension following spinal anesthesia. In the study, they did not observe any difference in the incidence of hypotension between

Table 3: Mean systolic and diastolic blood pressure and heart rate in times measured between the two studied groups

	Systolic (mmHg)			Diastolic (mmHg)			Heart rate (*n*/min)		
Time (min)	Ephedrine	Phenylephrine	*P*	Ephedrine	Phenylephrine	*P*	Ephedrine	Phenylephrine	*P*
Basis	114.78±12.90	116.95±16.71	0.42	86.69±8.40	86.69±8.40	0.42	90.28±9.15	89.06±12.19	0.59
3	87.39±11.24	92.60±8.28	0.001*	74.89±11.32	79.82±8.50	0.02*	89.19±8.75	87.76±10.85	0.84
6	80.43±14.90	89.13±8.64	0.001*	72.71±9.81	78.52±9.37	0.05	88.17±6.84	86.02±9.89	0.22
9	76.30±13.88	85.97±12.97	0.001*	71.73±9.14	77.73±9.33	0.002*	77.47±11	76.93±11.3	0.81
15	95±8.09	98.91±17.79	0.17	79.54±10	81.04±9.65	0.46	75.3±11.7	73.8±11	0.54
20	103.15±12.79	104.13±14.84	0.71	85.39±7.50	87.13±8.76	0.31	75.90±11.30	73.50±11	0.32
25	102.71±12	103.26±13.50	0.80	83.21±8.64	84.95±7.08	0.29	77.70±11.50	74.90±12.20	0.33
30	101.30±11.47	101.52±12.10	0.93	82.56±10.37	84.06±8.18	0.44	76.70±12.40	76.60±2.40	0.87

Data shown Mean±Standard deviation, and used of independent sample *t* test

Table 4: The number of people receiving the repetition of vasopressor and atropine in the two studied groups (*n*)

Group	Repetition of vasopressor (%)	Receiving atropine (%)
Phenylephrine	4 (8.7)	6 (13)
Ephedrine	11 (23.9)	3 (6.5)
P	0.04*	0.24

Data shown *n* (%), and used of Fisher exact test

the two groups. Phenylephrine was used IV in our study which may signify the difference in the results obtained in other studies compared to our study that the decrease of average blood pressure was lower in the IV phenylephrine compared to that in ephedrine in 3, 6, and 9 min.[17] In 2011, Alday Muñoz *et al*. compared the effect of ephedrine and phenylephrine on the prevention of hypotension due to the spinal anesthesia. In their study, the ability of ephedrine and phenylephrine was proved the same in the prevention of hypotension during cesarean section which was different from our study. Due to the physiological changes during pregnancy including changes in intravascular volume, cardiac index and heart rate in pregnant women, the difference in the type of participated patients can affect the reaction of vasopressor drugs.[18] In 2009 in Brazil, Magalhães *et al*. evaluated the impact of ephedrine and phenylephrine on the prevention of hypotension in spinal anesthesia for cesarean section as well as its effects on fetus and found that ephedrine is more effective in the prevention of hypotension than phenylephrine which was different from what was observed in our study.[13] Aragão *et al*. conducted a study in 2014 in which they investigated the preventive effect of metaraminol, phenylephrine, and ephedrine to prevent and treat hypotension in cesarean section through spinal anesthesia. The incidence of hypotension and heart rate did not differ from each other which were different with our results. Taking atropine did not differ among the groups and the number of people who need for atropine injection also did not statistically differ between two our studied groups.[19]

This randomized prospective study compared the preventive effect of phenylephrine (50 μg IV) and ephedrine (10 mg IV) on preventing hypotension after spinal anesthesia for hip fracture repair surgery with each other. The obtained results showed that the average hypotension was lower in the group received phenylephrine and the difference was significant. To obtain better and more accurate results, various methods of using these drugs are recommended in different surgical procedures.

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Conflicts of interest
There are no conflicts of interest.

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