



10-1-2020

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How to Cite This Article

Abd Elraziq, Bassem; Ali, Sohair; Abotaleb, Usama; and Alqassas, Mohammad (2020) "Norepinephrine versus Ephedrine in Prevention of Hypotension after Spinal Anesthesia," *Al-Azhar International Medical Journal*: Vol. 1: Iss. 10, Article 6.

DOI: <https://doi.org/10.21608/aimj.2020.39968.1308>

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Norepinephrine versus Ephedrine in Prevention of Hypotension after Spinal Anesthesia

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Received for publication August 29, 2020; Accepted November 08, 2020; Published online November 08, 2020.

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doi: 10.21608/aimj.2020.39968.1308

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ABSTRACT

Background: There is increasing attitude to use norepinephrine for prevention of spinal hypotension. Though, data is not adequate for routine use in clinical practice.

Aim of work: This study was aimed to compare the effectiveness and safety of norepinephrine infusion versus ephedrine infusion for prevention of spinal hypotension. The primary outcome was maintaining systolic blood pressure changes within 20% of baseline.

Patient and Methods: In our prospective double-blinded randomized study, we studied 130 patients, underwent elective surgeries under spinal anesthesia. Patients were randomly divided into two equal groups: Ephedrine group; received ephedrine (5mg/ml), and Norepinephrine group; received norepinephrine (5µg/ml). After spinal anesthesia, the study drug was started at a rate 30ml/h and adjusted according to blood pressure. Hypotension was treated by 1 ml bolus of the study drug. We assessed; systolic blood pressure, heart rate, total volume of infusion, need for boluses, and complications.

Results: Systolic blood pressure decreased in both groups in comparison to baseline at 2, 4, 6, and 8 minutes. When comparing both groups; blood pressure was lower in ephedrine group after 2 and 4 minutes, after that both groups were comparable. There was increase in heart rate in the 1st 10 minutes in ephedrine group. Attacks of tachycardia and hypertension occurred more in ephedrine group, but no differences regarding volume of infusion, need for boluses, attacks of bradycardia or hypotension.

Conclusion: both drugs are effective in prevention of spinal hypotension, but norepinephrine has a faster onset with fewer episodes of tachycardia and hypertension leading to better hemodynamic stability.

Keywords: Ephedrine; Hypotension; Norepinephrine; Prevention; Spinal.

Disclosure: The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.

Authorship: All authors have a substantial contribution to the article.

INTRODUCTION

Spinal anesthesia is the ideal anesthetic technique for a variety of surgical procedures.¹ It provides a fast, symmetrical, and intense sensory and motor block of high quality.

However, it can result in hypotension. Severe or sustained hypotension may cause nausea and vomiting, ischemia of vital organs, and circulatory collapse.¹

There are many mechanisms for hypotension during spinal anesthesia, however, the primary mechanism is decrease of peripheral vascular resistance due to preganglionic sympathetic block produced by spinal block.²

Sympathetic block produces hypotension through its effects on preload, afterload, contractility, and decrease heart rate. Preload is reduced by sympathetic block mediated vasodilatation, causing pooling of blood in the peripheries, and decreased venous return.³ Contractility can be affected by block of the upper thoracic sympathetic nerves.⁴

The impact of spinal block on Heart Rate (HR) is complicated. HR may increase (try to hypotension through the baroreceptor reflex) or decrease (either from sympathetic block of heart, or due to the reverse Bainbridge reflex).² The reverse Bainbridge reflex is decreased HR caused by reduced venous return.⁵

The typical cardiovascular response to spinal anesthesia is decrease of peripheral resistance, at first blood pressure is maintained by compensatory

increase in heart rate and stroke volume. However, due to complex multiple reasons, such as sympathetic blockade, and reduced venous return, this compensation usually fails to maintain blood pressure in the absence of proper intervention.⁴

Management of spinal hypotension should include frequent monitoring of blood pressure, fluid therapy, nonpharmacological methods, and vasopressors.⁶ Fluid therapy by crystalloids or colloids has been the traditional approach to restore volume and can be given as preload before block or co-load during and after the block. Nonpharmacological methods include positioning and leg compression. Trendelenburg position can increase venous return to the heart but also can lead to higher level of spinal anesthesia. The ideal is to elevate the upper half of the body with pillows below the shoulders while raising the lower limb. Leg compression by flexion of the hip, elastic bandages, or stockings.⁶

Because the rapid sympathetic block by spinal anesthesia provides not enough time for cardiovascular compensation,³ the efficient method to treat spinal hypotension is administration of vasopressors, either given by infusion or boluses.¹

Vasopressor drugs act by reversing the circulatory effect of sympathetic blockade. They also restore vascular tone and preserve venous return and cardiac filling.⁷

For several decades, intravenous ephedrine was used as a vasopressor of choice in management of spinal hypotension. It has an indirectly acting sympathomimetic effect, and α and β direct adrenergic receptor agonist effect.¹ It maintains arterial pressure by increases in cardiac output (CO) and HR because of its β adrenergic receptor agonist effect and increase peripheral vascular resistance because of its α adrenergic receptor agonist activity. Prophylactic use of ephedrine was also effective.

However, several adverse effects must be in mind while administering ephedrine such as tachyphylaxis, arrhythmia, hypertensive episodes, tachycardia, increased myocardial contractility, and oxygen demand.¹

Recent studies suggested the traditional vasopressor norepinephrine may represent a potential alternative to manage or prevent spinal hypotension, it has attracted increasing attention. Norepinephrine has a potent α adrenergic effect and weak β adrenergic effect; consequently, it reduces the risk of tachycardia and arrhythmia.^{7,8,9} Additionally, it has a shorter onset time (<1 minute) than ephedrine (\approx 3 minutes), thus may correct hypotension at a faster rate.¹

However, data in this area is not sufficient and more studies are recommended before its routine use in clinical practice.

There have been some researches indicating the effective and safe use of norepinephrine to treat or prevent spinal hypotension; however, most of these studies have been performed in comparison to phenylephrine or compared to ephedrine but used IV

boluses, not infusion. To our knowledge, there is little information available comparing norepinephrine versus ephedrine infusion for prevention of hypotension during spinal anesthesia.¹ Considering this limited data availability, we performed our study.

The study aimed to evaluate the effectiveness and safety of prophylactic infusion of norepinephrine versus ephedrine for prevention or minimization of spinal hypotension. The primary outcome was prevention of hypotension as measured by systolic blood pressure changes within 20% of baseline. Secondary outcomes were effect on heart rate, need for bolus dose, and incidence of complications.

Sample size :

It was calculated Using G* Power 3.1.9.2 program, Kiel, Germany; depending on our primary outcome (blood pressure after spinal) In a previous study¹ the blood pressure after spinal was 91.4 ± 9.5 mmHg in patients treated with norepinephrine and 87.2 ± 9.6 mmHg in patients treated with ephedrine, we planned our study in order to detect 5% significance level (α) at a power of 80% (1- β). The minimum sample size was to study 65 patients in each group.

PATIENT AND METHODS

After local ethics committee approval this prospective double blinded randomized comparative study was conducted from 1 July 2019 to 31 March 2020 in Al-Hussein University hospital. One hundred thirty patients, ASA physical status <3, aged from 21 to 50 years, and weighing from 60 to 90 kg underwent elective surgical procedure below the umbilicus under spinal anesthesia were included in the study after obtaining informed written consent.

We excluded any patient with baseline systolic blood pressure (SBP) > 140 mmHg, obese patients with BMI > 30 Kg/m², patients with increased intra-abdominal pressure, patients with cardiovascular, cerebrovascular diseases, impaired renal or hepatic functions.

Also, patients who refused spinal or to participate in the study, patient with congenital or developmental spine abnormality, thrombocytopenia, coagulation defects, or any contraindication to spinal block, were excluded from the study.

Using computer generated randomization and sealed opaque envelope, patients were randomly divided into two groups (65 patients each) depending on the study drug given: Ephedrine group; received ephedrine (5 mg/ml) diluted with saline in 20 ml syringe, and Norepinephrine group; received norepinephrine (5 μ g/ml) diluted with saline in 20 ml syringe.

After arrival to the operating room, baseline BP and HR were measured, an IV wide bore cannula was inserted, but no pre-load was provided.

In the sitting position, and after disinfection of the skin, 2 mL lidocaine 1% was infiltrated and spinal anesthesia was administered using 25-gauge spinal

needle at L3–4 intervertebral space. After verifying clear cerebrospinal fluid, 3 mL of hyperbaric bupivacaine 0.5% (15 mg) were injected, and the patient returned to supine decubitus. Rapid IV co-load (15 ml/kg lactated Ringer) were given over 15–20 minutes, after that the IV fluid was reduced to 5mL/Kg/h. Block-level were evaluated using ice; the upper dermatomal level of block 5 minutes after intrathecal injection were recorded and compared.

Immediately after spinal anesthesia, the study drug was started at a rate of 30 ml/h, it was administered and adjusted by the anesthesiologist, who was blinded to the infused drug. Study drug was placed in a syringe pump that was connected to a 3-way stopcock attached directly to the patient's cannula using a low volume line .

Heart rate and Noninvasive BP monitoring were assessed every 2 minutes till 10 minutes then every 5 minutes.

After each BP measurement, infusion was readjusted by the anesthesiologist, according to our study schedule (Table 1).

After 15 minutes of stability (SBP> 90% of baseline), infusion went step down (i.e. infusion stopped if SBP> 100% of baseline, and decreased to 15 ml/h if SBP [90-100%] of baseline, then stopped after another 15 minutes of stability) .

Hypotension was treated by 1 ml IV bolus of the study drug. Bradycardia was treated with IV 0.5 mg atropine and could be repeated after 3 minutes.

Hypotension was defined as SBP <80% of the baseline value, Hypertension was defined as SBP >120% of the baseline, tachycardia was defined as HR >120 beat per minute (bpm), and bradycardia was defined as HR <60 bpm.

We assessed; total volume of infusion needed, a number of boluses and number of patients needed boluses, time to stop infusion, and need for atropine.

Systolic Blood Pressure % of Baseline	Infusion Rate (ml/h)	Norepinephrine Delivery Rate in Infusion Group I (µg/min)	Ephedrine Delivery Rate in Infusion Group II (mg/min)
>110	0	0	0
100–110	15	1.25	1.25
90–99	30	2.5	2.5
80–89	45	3.75	3.75
<80	60	5	5

Table 1: Infusion schedule.

Attacks of tachycardia, hypertension, bradycardia, hypotension, or nausea and vomiting were also recorded and compared.

Statistical analysis:

SPSS version 17 program was used to enter data and statistical analysis. Data were presented as mean±SD, median (Inter Quartile Range), range, and number of patients. For parametric data, comparison between the two groups was performed using unpaired t-test while paired t-test was performed for comparisons within the same group. Mann-Whitney test was performed for nonparametric ordinal data. For data collected as number of patients; Fisher exact test was performed. A P-value <0.05 was considered statistically significant.

Results

There were no significant differences regarding patients' characteristics and level of spinal block (Table: 2).

There was a statistically significant increase in heart rate in the 1st 10 minutes in ephedrine group patients, after that there were no significant differences (Table: 3).

There was a significant decrease in systolic blood pressure in both groups in comparison to baseline at 2, 4, 6, and 8 minutes. When comparing both groups; there was significantly lower systolic blood pressure in ephedrine group after 2 and 4 minutes, after that both groups were comparable (Table: 4).

There were no significant differences regarding total volume of infusion, need for boluses, time till stop infusion, or need for atropine (Table: 5).

Attacks of tachycardia and hypertension occurred more significantly in ephedrine group, but no significant differences regarding attacks of bradycardia, hypotension, or nausea and vomiting. When hypotension occurred; time till 1st episode was significantly shorter in ephedrine group (Table: 6).

		Group E (n=65)	Group NE (n=65)	P-value
Age (years)		43.9±11.54	40.8±11.09	>0.05
Weight (kg)		77.38±9.71	73.48±10.15	>0.05
Height (cm)		169.4±9.69	168.6±7.45	>0.05
Sex	male	37	35	>0.05
	female	28	30	
ASA	I	33	37	>0.05
	II	32	28	
Level of spinal block		T6(T5-T9)	T6(T6-T9)	>0.05

Table 2: Patients characteristics and level of spinal (Data are expressed as mean±SD, number, and median) (Inter Quartile Range).

	Group E (n=65)	Group NE (n=65)	P-value
Base line	79.3±11.1	83.3±14.1	>0.05
2 min	86.3±13.2	79.1±15.6	>0.05
4 min	94.2±20	81.1±14.8	<0.001
6 min	99.2±22.3	80.9±14.1	<0.001
8 min	98.7±18.9	82.7±13.4	<0.001
10 min	94.7±19.8	81.8±14.5	<0.001
15 min	84.3±17.4	82.6±11.3	>0.05
20 min	77.1±14.2	78±11.6	>0.05
25 min	76.3±14.2	77.9±10.2	>0.05
30 min	75.4±8.8	76.9±10	>0.05
35 min	75.6±9.8	77±10	>0.05
40 min	77.4±10.4	76.2±10.7	>0.05
45 min	78.1±11.2	79.2±13.8	>0.05
50 min	76.7±12	79.2±12.6	>0.05
55 min	79±15	81.8±16.3	>0.05
60 min	77.3±11.1	80.4±13.3	>0.05

Table 3: Heart rate (beat/min) (Data are expressed as mean±SD.).

	Group E (n=65)	Group NE (n=65)	P-value
Total volume of infusion (ml)	10.85±5.07	11.54±5.33	>0.05
Number of boluses	1(1-2)	1(1-2)	>0.05
Number of patients need boluses	13	17	>0.05
Time till stop infusion (min)	26.5±13.8	27.2±13.3	>0.05
Atropine (mg)	0.5(0.5-0.5)	0.5(0.5-1)	>0.05
Number of patients need Atropine	1	4	>0.05

Table 5: Drugs used in both groups (Data are expressed as mean±SD, median (Range), and number of patients).

Hypotension is a major threat following administration of spinal anesthesia that may require emergency management. Many methods have been studied to prevent spinal hypotension, e.g., fluid preload, vasopressors, or combination. The clinical outcomes of fluid preload for prevention of spinal hypotension were not satisfactory in many clinical trials, thus, authors have turned their attention to vasopressor drugs.¹⁰

	Group E (n=65)	Group NE (n=65)	P-value
Base line	123.4±9.2	121.1±9.1	>0.05
2 min	106.5±8.4	110.2±10.1	<0.05
4 min	108.5±9.8	112.7±11.1	<0.05
6 min	111.3±9.4	113.7±10.3	>0.05
8 min	118.3±15	115.5±15.5	>0.05
10 min	120.7±18.4	117.3±16.4	>0.05
15 min	123.9±15.8	119.3±10.6	>0.05
20 min	121.8±9.6	119.7±8.7	>0.05
25 min	122.5±8.1	119.5±8.1	>0.05
30 min	125±7.7	123.2±9.1	>0.05
35 min	123.9±11.3	120.3±9.7	>0.05
40 min	124±9.4	124.4±14.4	>0.05
45 min	122.1±8.9	120.3±9.7	>0.05
50 min	124.2±10.3	121.1±7.3	>0.05
55 min	122.5±8.2	119.6±7.1	>0.05
60 min	126.1±9.3	122.8±8.1	>0.05

Table 4: Systolic blood pressure (mmHg) (Data are expressed as mean±SD.).

	Group E (n=65)	Group NE (n=65)	P-value
Tachycardia	8	1	<0.05
Bradycardia	1	4	>0.05
Hypertension	13	4	<0.05
Hypotension	13	17	>0.05
Time till 1st episode of hypotension (min)	5.1±2.3	8.8±4	<0.05
Nausea or Vomiting	3	2	>0.05

Table 6: Complications (Data are expressed as mean±SD and number of patients).

This study compared the effect of infusion of norepinephrine versus ephedrine to prevent hypotension during spinal anesthesia. The findings of present study confirmed that both drugs are effective in prevention of hypotension during spinal anesthesia. Norepinephrine had faster onset with rapid and superior hemodynamic stability compared with ephedrine by maintaining stable blood pressure and HR with fewer episodes of tachycardia, and hypertension.

Vasopressor drugs are effective in prevention and management of post-spinal hypotension, but there is

a debate in the choice; ephedrine and phenylephrine are the drugs of choice. Ephedrine has been the gold standard vasopressor, it is safe, available, and familiar to most anesthesiologists. It causes peripheral vasoconstriction leading to elevation of blood pressure, and an increase in myocardial contractility, HR, and therefore cardiac output.^{7,10}

Phenylephrine is a short-acting, potent vasopressor that causes elevation of both systolic and diastolic blood pressure. It is used as a second choice, but some anesthesiologists used it as a 1st line vasopressor, especially in cesarean deliveries. However, phenylephrine has clinically significant bradycardia with a resulting decrease in cardiac output.⁷

Recent studies investigated norepinephrine for prevention of hypotension during spinal anesthesia with good results. Norepinephrine immediately antagonizes the effect of the sympathetic block and may be more appropriate for preserving blood pressure with less negative effects on HR and cardiac output.¹¹

Elnabity and Selim¹⁰ performed their study during cesarean section, they compared prophylactic boluses of norepinephrine and ephedrine at the time of spinal anesthesia, and more on-demand boluses if hypotension occurred, also, did not use baseline infusion. Our results agreed with most of their results, although baseline infusion of the vasopressor drugs leads to more hemodynamic stability and less need for boluses. They chose the intermittent IV boluses regimen because of its availability in daily clinical practice and familiarity with most of the anesthesiologists. But they reported more bradycardia in patients treated with ephedrine, which is against our study.

On the other hand, El Shafei, et al.¹² compared norepinephrine versus ephedrine to manage hypotension during spinal anesthesia in ischemic heart disease patients undergoing knee arthroscopic surgeries. They established that norepinephrine has faster onset compared with ephedrine in control of hypotension with less tachycardia, which is useful in these patients. These results agreed with our results, however, they found no difference between the two drugs regarding the incidence of hypertension, and this is not in agreement with our study as we found higher number of hypertensive episodes in patients treated with ephedrine. To be noted these two studies were conducted on different categories of patients.

Ngan Kee et al.¹¹ compared the prophylactic IV norepinephrine infusion versus boluses given to treat hypotension in cesarean section patients. The results showed the superiority of norepinephrine infusion over the intermittent boluses as regard hemodynamic stability.

Many researchers studied the usage of norepinephrine for prevention of hypotension during spinal block and used many doses and regimens of administration. Onwochei, et al.¹³ investigated the effect of different doses of norepinephrine boluses, while Chen, et al.¹⁴ and Hasanin, et al.¹⁵ studied different doses of norepinephrine infusion. The results were that; norepinephrine preserves blood pressure without significant side effects. The starting dose we used is the average accepted dose in these studies and we adjust according to response.

Many other studies compared the effect of norepinephrine or ephedrine with phenylephrine for preserving blood pressure during spinal anesthesia.

Ngan Kee, et al.⁷ compared preventive outcome of norepinephrine infusion with that of phenylephrine infusion in patients receiving spinal anesthesia for cesarean section, they found that norepinephrine produces better HR and cardiac output with comparable efficiency for preserving blood pressure compared to phenylephrine.

However, Vallejo, et al.¹⁶ found that all hemodynamic parameters including HR, blood pressure, cardiac output, and stroke volume, were similar in both drugs. They also used a fixed-rate infusion.

Sharkey et al.¹⁷ compared IV phenylephrine versus norepinephrine boluses to manage hypotension during spinal anesthesia. Patients requiring additional rescue boluses and the risk of bradycardia episodes were higher in phenylephrine group compared to norepinephrine group.

Both Dong, et al.¹⁸ and Wang, et al.⁴ studies compared prophylactic bolus of norepinephrine and phenylephrine on spinal hypotension. They found that both norepinephrine and phenylephrine are effective in avoiding spinal hypotension with less undesirable effects of norepinephrine on HR and cardiac output than phenylephrine.

Many Authors studied ephedrine versus phenylephrine for treatment of spinal hypotension, of these studies Gunda et al.;¹⁹ they evaluated the efficacy and safety of ephedrine, in comparison to phenylephrine given to treat spinal hypotension during cesarean deliveries and established no significant difference, as like as Naghibi, et al.²⁰ who compared both drugs, for spinal hypotension during elective lower abdominal surgeries, there was no difference between both drugs in preserving BP with more episodes of bradycardia in patients receiving phenylephrine

Limitation of our study includes that we did not extend observation for the postoperative period and further studies are needed to detect remote complications.

CONCLUSION

both ephedrine and norepinephrine are effective in prevention of hypotension during spinal anesthesia, but norepinephrine has faster onset with rapid and better hemodynamic stability by maintaining stable blood pressure and HR with fewer episodes of tachycardia and hypertension. Norepinephrine can be used in daily practice for management of hypotension during spinal anesthesia.

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