Original Article

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# Comparison between ephedrine and noradrenaline in Prevention hypotension after spinal anesthesia in cesarean section: A prospective randomized comparative clinical study

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## Abstract

Background: Ephedrine and norepinephrine considered an option to maintain maternal blood pressure during spinal anesthesia (SA) since hypotension is considered a common consequence of SA. The aim of the current study is the assessment of the maternal and neonatal safety and efficacy of norepinephrine compared to ephedrine in treatment of SA induced hypotension in cesarian delivery. Patients and Methods: 100 healthy individuals under spinal anesthesia for a cesarean delivery were selected at random to Group N (n = 50). They either got Group E (n = 50) or a 1 mL bolus of intravenous norepinephrine with a density of 10 g/ 1 mL. To maintain their systolic blood pressure, 1 mL of intravenous ephedrine with a density of 5 mg/mL was given to them. The dose of vasopressor boluses used the Apgar score, and maternal hemodynamic elements were all recorded. Results: When compared to Group E, Group N had considerably fewer instances of maternal hypotension, hypertension, and bradycardia and tachycardia. Conclusions: A suitable and safe drug to counteract the hemodynamic effects of spinal anesthesia during cesarean delivery is norepinephrine.

**Keywords:**

Spinal anesthesia, Ephedrine, Norepinephrine, Cesarean section.

## Introduction

The first local anesthetic discovered during the steps of creating regional anesthesia was cocaine, which is the only local anesthetic that occurs naturally. The first spinal anesthesia operation was conducted in 1898 in Germany by August Bier. Spinal anesthesia was the first regional anesthetic treatment to be used. Prior to this, the only choices for local anesthetic techniques were infiltration anesthesia and topical anesthetic for the eyes. The brain and spinal cord make up the central nervous system (CNS). The use of local anesthetic to the CNS or the area around it is referred to to as neuraxial anesthesia. A local anesthetic is injected right into the intrathecal space (subarachnoid space) during spinal anesthesia, a kind of neuraxial anesthesia.

The sterile cerebrospinal fluid (CSF), an opaque fluid that surrounding the brain and spinal cord, is kept in the subarachnoid space. A typical adult human has 130 to 140 mL of CSF, which circulates continually throughout the day. Every day, 500 mL of CSF is produced.

The caudal and epidural anesthetic techniques are further neuraxial techniques each with a specific indication .Only the lumbar spine undergoes spinal anesthesia, which is utilized for procedures on the lower abdomen, pelvis, and lower extremities.

## Anatomy and Physiology

For the physician to provide spinal anesthesia, the patient needs to be set properly and have a basic knowledge of neuraxial anatomy. Intrathecal (subarachnoid) space anesthetic delivery with the correct dose is the objective.

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Seven cervical, 12 thoracic, five lumbar, and five fused sacral vertebrae make up the spine .Due to their distinct structure and relative placements, the various spinal bones have distinctive ligaments, and other structures. Spinal cord is housed in this canal. Through lateral gaps produced between pedicles from adjacent vertebrae, the spinal nerves reach the spinal canal [1-3].

## Indications

For a lot of surgeries executed below the neck, neuraxial anesthesia is utilized either alone or in combination with a general anesthetic. Patients must understand that while spinal anesthesia provides effective pain relief and muscle relaxation during the surgical procedure, they will likely experience temporary loss of sensation and movement in the lower part of their body until the anesthetic block wears off [4]. This loss of sensation should not cause lasting harm, and patients can expect a gradual return of normal function once the effects of the anesthesia have dissipated. Spinal anesthesia is frequently used for surgical procedures impacting the lower belly, pelvis, perineum, and lower extremities and is useful for surgical procedures below the umbilicus, as was indicated in the introduction [5, 6].

Informed patient consent must be signed and information regarding the procedure is required. The indication for spinal anesthesia, what to anticipate during neuraxial installation, hazards, and other information are all essential as the procedure is typically carried out on awake or barely sedated patients [7]. Some of the topics that may reduce anxiety involve its benefits and possible solutions. Patients must be informed that until the block releases, they will have little to no motion in their lower extremities. For quick procedures, spinal anesthesia is ideal. General anesthesia is usually preferred for prolonged procedures or ones that can endanger breathing [8].

## Contraindications

Spinal and epidural neuraxial anesthesia have several well-known contraindications. Absolute contraindications include the patient's lack of consent, high intracranial pressure (ICP), which is usually produced by an intracranial mass, and infection at the surgery site (risk of meningitis) [9, 10]. Relative contraindications include [11, 12]: - Pre-existing neurological diseases, especially those that fluctuate in intensity, like MS (multiple sclerosis). - Hypovolemia caused by severe dehydration, which could be caused by hypotension. Age between 40 and 50, emergency surgery, obesity, persistent alcohol use, hypovolemia, and age between 40 and 50 are all risk factors for hypotension. - Given the danger of epidural hematoma with epidural anesthesia, thrombocytopenia or coagulopathy is particularly common [13].

-Other relative contraindications are essential mitral and aortic stenosis and left ventricular outflow blockage as observed with hypertrophic obstructive cardiomyopathy. Neuraxial block placement must be examined in cases of coagulopathy [14].

The American Society of Regional Anesthesia (ASRA) has updated guidelines that describe the time for neuraxial anesthesia for patients using oral anticoagulants, antiplatelets, thrombolytic treatment, unfractionated, and low molecular weight heparin. Before starting the process, review the most recent recommendations.

## Aim of the study

The comparison of NE and EP for treating spinal anesthesia-induced hypotension in a cesarean delivery to determine which is more secure and efficient for women.

# Material and Methods

## Study design

A prospective, randomized single blinded clinical study, that involved 100 participants, they were divided into two groups:

1.Group N: received norepinephrine.
2.Group E: received ephedrine.

When MAP fell below 60 mmHg, an intervention was given. Hypotension was defined as a >20% drop from the original value of MAP.

## Study setting

The research was conducted at Habboubi Teaching Hospital in Nasiriyah Governorate in Iraq, and it lasted from December 2022 until May 2023.

## Size of the sample

The study was conducted over a six-month period at two tertiary care centers. Patients were randomly assigned to either the intervention or control group. Data collection included maternal age, gestational age, baseline blood pressure, number of vasopressor boluses, neonatal outcomes, and adverse events related to vasopressor use. Statistical analysis was performed using appropriate tests for comparing continuous and categorical variables.

The findings of this investigation will contribute to the existing literature on vasopressor usage in the peripartum period and aid in optimizing maternal and neonatal outcomes. The number of boluses of vasopressors required to maintain maternal blood pressure was the primary outcome of this investigation, and the sample size calculation was based on a pilot trial including 20 patients.

The minimal sample size needed to show a statistically significant difference in the number of boluses of vasopressors between the two groups was 49 patients per group, assuming the confidence interval 95% and test power of 80%. We included 100 patients—50 in each

group—taking the projected dropout rate into account.

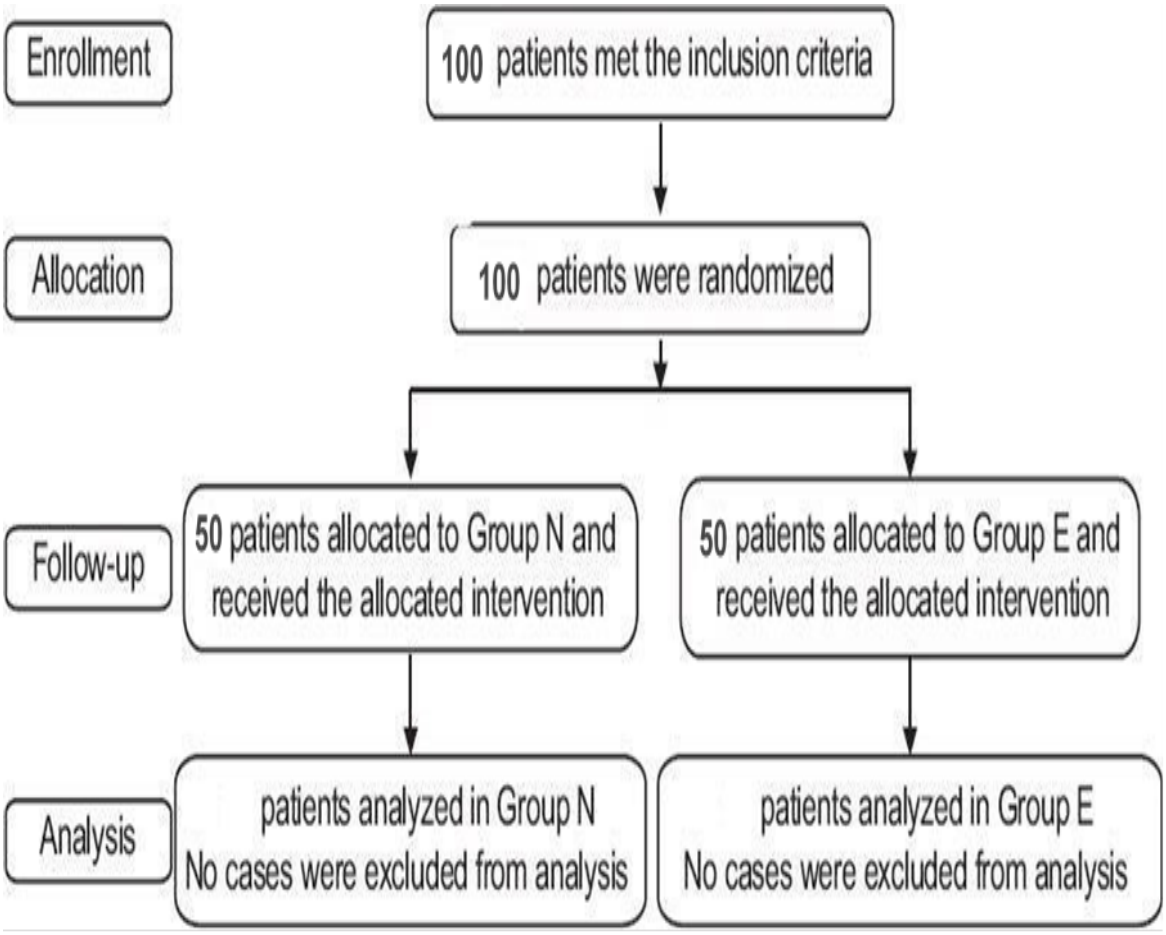


**Figure 1**

### Inclusion criteria

1. ASA(I-II)
2. Age (18 – 40 years)
3. Full-term pregnancy
4. Elective caesarian surgery

### Exclusion criteria

1. Lack of cooperation
2. Patients refused to be included in the study
3. Patients with spinal deformities
4. Patients are of short stature
5. failed spinal anesthesia
6. Morbid obesity (BMI≥35 kg/m$^2$)
7. Coagulopathy, or on anticoagulation therapy
8. History of allergies to any medication used in the study

## Results

### Demographic and maternal characteristics

The study included 100 participants, which were divided into two groups, the first group received ephedrine [EP] (50 patients), and the other group received norepinephrine [NE] (50 patients). There was no significant difference in age, BMI, gravida, and gestational age, as illustrated by table 1.1. At the beginning of the study, the two groups were comparable in terms of these key demographic and clinical characteristics

**Table 1.1: Assessment of demographic and maternal characteristics Assessment of systolic blood pressure (SBP)**

| Variables | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Age (y), mean ± SD | 28.22±6.31 | 30.46±6.20 | 0.076 |
| BMI (kg/m$^2$), mean ± SD | 28.47±3.85 | 28.68±4.19 | 0.795 |
| Gravida, n (%) | | | |
| Primigravida | 16 (32.0%) | 13 (26.0%) | 0.509 |
| Pluripara | 34 (68.0%) | 37 (74.0%) | |
| Gestational age (weeks), mean ± SD | 38.30±0.95 | 38.16±1.08 | 0.493 |

SD: standard deviation, y: year, n: number

There was no significant difference in SBP at baseline and after 5 minutes, afterward SBP was significantly

higher in norepinephrine at 10, 15, 30, and 60 minutes, as illustrated by table 1.2 and figure 1.1.

**Table 1.2: Assessment of systolic blood pressure (mmHg)**

| Time | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Baseline | 107.78±9.59 | 105.44±10.96 | 0.259 |
| 5 min | 97.40±10.63 | 97.14±11.29 | 0.906 |
| 10 min | 89.80±11.13 | 99.12±11.31 | <0.001 |
| 15 min | 89.96±11.70 | 98.82±12.34 | <0.001 |
| 30 min | 93.96±10.65 | 102.78±12.87 | <0.001 |
| 60 min | 102.86±12.89 | 111.14±14.65 | 0.003 |

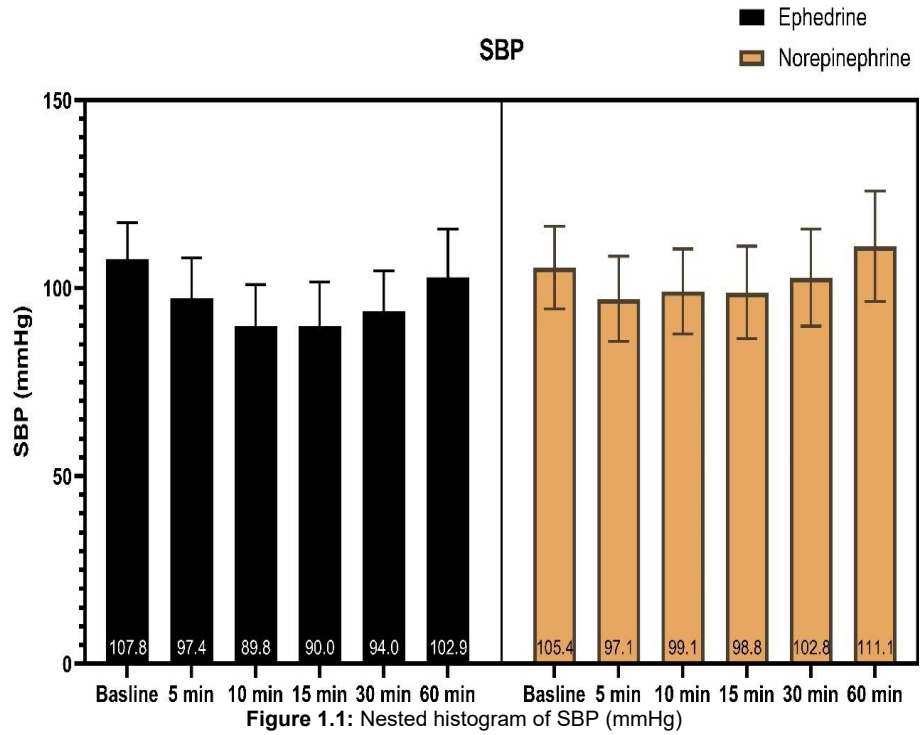


**Figure 1.1:** Nested histogram of SBP (mmHg)

## Assessment of diastolic blood pressure (DBP)

Assessment of diastolic blood pressure is typically performed using a sphygmomanometer, commonly known as a blood pressure cuff, along with a stethoscope.

The cuff is inflated to a level exceeding the systolic blood pressure and then gradually released while listening for the characteristic sounds of Korotkoff. The point at which these sounds disappear corresponds to the diastolic blood pressure, providing a reliable measurement of this vital parameter. There was no significant difference in DBP from baseline till 60 minutes of follow- up, as illustrated by table 1.3.

**Table 1.3: Assessment of DBP (mmHg)**

| Time | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Baseline | 78.28±6.99 | 79.24±7.06 | 0.496 |
| 5 min | 63.32±9.87 | 63.66±9.95 | 0.864 |
| 10 min | 60.34±10.22 | 61.42±10.17 | 0.598 |
| 15 min | 63.34±11.58 | 64.22±11.94 | 0.709 |
| 30 min | 73.46±13.14 | 72.98±14.23 | 0.861 |
| 60 min | 82.30±14.42 | 81.22±17.64 | 0.738 |

## Assessment of mean arterial blood pressure (MBP)

Only after 15 minutes MBP was significantly higher in norepinephrine, while at the rest of the time period no significant difference was observed, as illustrated by table 1.4 and figure 1.3. These results suggest that the two groups responded differently in terms of mean blood pressure changes, particularly at the 15-minute mark.

It's important to consider the implications of this difference in MBP between the ephedrine and norepinephrine groups and to explore the potential

clinical significance of the observed variation at the specified time point

**Table 1.4: Assessment of mean blood pressure (mmHg)**

| Time | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Baseline | 88.12±5.13 | 87.98±5.73 | 0.901 |
| 5 min | 74.69±7.31 | 74.82±7.70 | 0.927 |
| 10 min | 70.16±7.52 | 73.99±7.99 | 0.015 |
| 15 min | 72.21±8.71 | 75.75±9.08 | 0.049 |
| 30 min | 80.30±10.00 | 82.91±10.45 | 0.204 |
| 60 min | 89.15±10.77 | 91.20±12.79 | 0.389 |

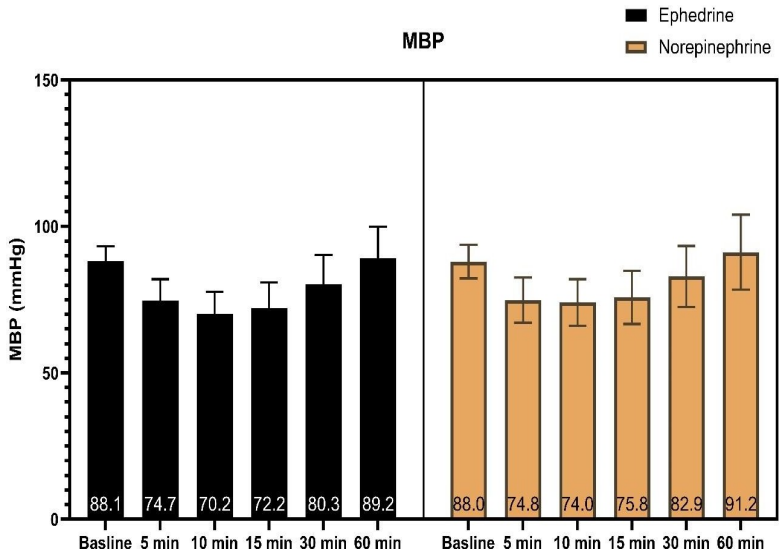


**Figure 1.3:** Nested histogram of MBP (mmHg)

## Assessment of heart rate (HR)

Heart rate was significantly lower in norepinephrine group from 5 minutes till the end of 60 minutes of follow-up, as illustrated by table 1.5 and figure 1.4.

**Table 1.5: Assessment of heart rate (beat/min)**

| Time | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Baseline | 89.60±10.20 | 92.44±11.33 | 0.191 |
| 5 min | 104.52±11.27 | 88.52±11.42 | <0.001 |
| 10 min | 110.84±11.96 | 84.04±11.39 | <0.001 |
| 15 min | 117.48±12.69 | 79.92±11.60 | <0.001 |
| 30 min | 111.96±12.65 | 73.48±11.32 | <0.001 |
| 60 min | 117.22±12.57 | 71.02±11.09 | <0.001 |

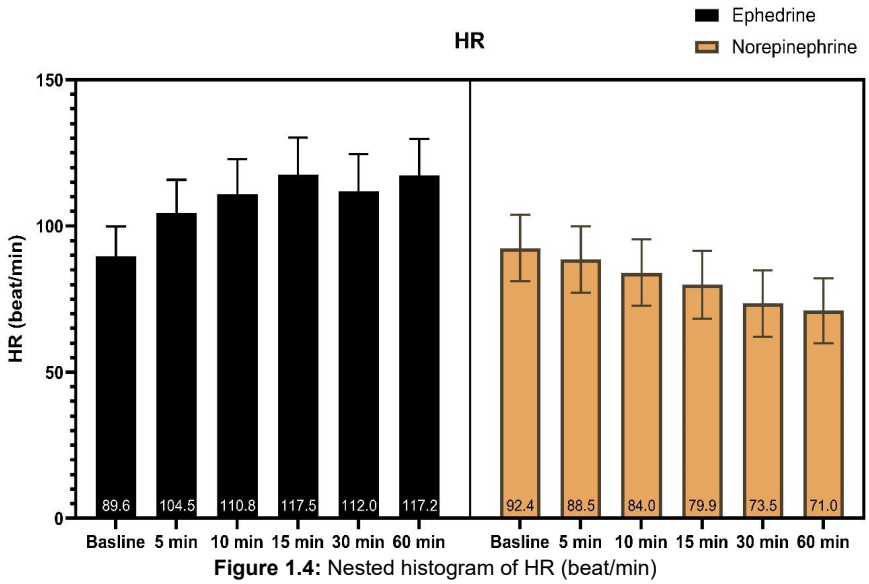


**Figure 1.4:** Nested histogram of HR (beat/min)

### Assessment of partial oxygen saturation (%)

There was no significant difference in SPO between both groups at all time periods, as illustrated by table 1.6.

**Table 1.6: Assessment of SPO2**

| Time | Ephedrine | Norepinephrine | p-value |
|---|---|---|---|
| Number | 50 | 50 | - |
| Baseline | 98.52±1.13 | 98.52±1.13 | 0.999 |
| 5 min | 98.48±1.07 | 98.62±1.18 | 0.536 |
| 10 min | 98.52±1.23 | 98.52±1.11 | 0.999 |
| 15 min | 98.40±1.16 | 98.62±1.16 | 0.345 |
| 30 min | 98.40±1.21 | 98.58±1.13 | 0.444 |
| 60 min | 98.42±1.14 | 98.36±1.14 | 0.793 |

## Discussion

### Main results hypotension and hemodynamic stability

In the present study the incidence of postanesthetic hypotension was significantly lower in women received norepinephrine (NE) compared to ephedrine (EP) (34%, vs. 54%, p-value = 0.044), with absolute risk reduction of 56.1% in the incidence of hypotension, this covers the incidence at any time period. In more detailed assessment after 10 minutes the incidence of hypotension was significantly lower in NE compared to EP (30, vs. 52%, p- value = 0.025). for the rest of the time periods there were no significant difference between both groups, despite the incidence of hypotension is lower in NE in most of the time periods. In this study, we chose these five times (5, 10, 15, 30, and 60 minutes) when the blood flow is usually unstable, this instability after spinal anesthesia was started is related to the systemic vascular resistance went down, but the cardiac output, heart rate, and stroke volume all went up by a small amount [15]. In term of hemodynamic stability, systolic blood pressure was significantly higher in NE compared to EP (at 10, 15, 30, and 60 minutes), diastolic blood pressure was not different between both groups at all time periods, mean blood pressure was significantly higher in NE compared to EP (at 10 and 15 minutes). Heart rate was significantly lower in NE compared to EP.

This indicate that NE offer better safety profile compared to EP, which is added to its better outcome to prevent hypotension in post-spinal anesthesia procedures. In terms of need for rescue analgesia, there was no significant difference between both NE and EP in that aspect, of notice the numerical value was lower in NE compared to EP (12% vs. 6%, p-value = 0.487), however it did not reach a statistical significance. In 2015, Ngan Kee et al. [16] were the first to conclude that NE was used to preserve blood pressure constant throughout the experiment during spinal anesthesia during cesarean deliveries. By using computer-controlled infusion, they showed that NE raised the heart rate and cardiac output more than phenylephrine did but had the same effect on lowering blood pressure.

A RCT (randomized clinical trial), done in Iran, 56 hypertensive patients were divided into two groups (each 28 patients) according to antihypertensive drug (either NE or EP) all patients received SA (spinal anesthesia) and were followed up prospectively. When compared to EP, NE had a significantly lower incidence of hypotension, a significantly higher MAP, a significantly lower HR, and a significantly lower number of rescue vasopressor boluses used throughout the SA. These findings were in agreement with the current study. A study that examined the bolus doses of NE (4 μg) and EP (4 mg) for hypotension prevention in CS, they found that HR was significantly higher in NE [17]. The hypotensive impact of spinal anesthesia after cesarean birth was studied by S. Xu et al., who compared intravenous boluses of EP and NE as a treatment. They demonstrated that NE was superior to EP in terms of maintaining blood flow in the uterine artery and maternal blood pressure. Additionally, NE was associated with fewer episodes of hypotension and hypertension, as well as a lower incidence of bradycardia and tachycardia. Furthermore, it needed a lower total number of boluses [18]. Which is in agreement with the current study. SBP was significantly higher in NE compared to EP at 2 and 4 minutes afterwards till 1 hour of follow-up no significant difference was found, HR was significantly lower in NE compared to EP at 4-, 6-, 8-, and 10-minutes afterwards till 1 hour of follow-up no significant difference was found [19].

A study examined that 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$ NE infusion for 30 minutes, compared to 0.15 mg/kg EP bolus, in 190 CS women hypotension was lower in NE compared to EP (29.5% vs. 44.9%, with 0.51, P-value = 0.034), SBP decrease was significantly higher in EP compared to NE, incidence of tachycardia was significantly in EP [20]. Which is in agreement with the current study. Another study shown that NE is efficient in maintaining systolic blood pressure with a drop in heart rate, which is beneficial for individuals who suffer from coronary artery disease [21]. Ephedrine stimulates the sympathetic nervous system and has potent inotropic and chronotropic effects on the heart. Its action might be either directly (by acting as an agonist for alpha or beta receptors) or indirectly (catecholamine, namely norepinephrine release). It lowers afterload, raises cardiac output, raises blood pressure and heart rate, and produces modest arteriolar constriction [22]. The vasoconstrictive impact of ephedrine is reduced with continued use of the drug. It has slow onset of action. Ephedrine has been linked to an increased risk of tachycardia, tachyphylaxis, and hypertension[23]. NE has both beta- and alpha-adrenergic effects (weak beta-adrenergic and potent alpha -adrenergic receptor agonist, which could lead to a higher heart rate and cardiac output than EP and a lower chance of bradycardia. It causes an arterial and venous vasoconstriction and improves venous return and cardiac preload. Several studies were in agreement with the current study findings, in which NE offer better

hemodynamic control than EP[24]. Because anesthesiologists typically use lumbar anesthesia to diffuse local anesthetics in order to achieve spinal nerve block during cesarean section, this practice can cause hypotension manifestations like decreased cardiac blood volume and vascular dilation in the anesthesia area. This is an urgent problem that needs to be solved in the field of obstetrics and gynecology [25]. Because more people know about cesarean sections, anesthesia, blood transfusions, and the balance of water and electricity, the number of cases of dystocia, such as cephalopelvic asymmetry, abnormal birth canals, and umbilical cord prolapse, has gone down by a large amount. This has greatly increased the safety of newborns and mothers. But lumbar anesthesia also causes vagal hyper function, which has serious effects on the mother's blood flow, breathing, and digestive systems [26]. In a study, that examine pregnant women that undergone CS with spinal anesthesia, two groups EP (40 women) and NE (40 women). They reported no significant differences in heart rate, while the SBP and DBP was significantly higher in NE compared to EP. Which is to the contrary to our findings in which no significant difference in SBP and DBP for both groups (this could be explained by the mode of use of NE in which both used as intermittent in our study while they used continues infusion for NE) [27].

Norepinephrine is a strong -receptor agonist that has a clear effect on skin, mucosal, and glomerular blood vessels by making them constrict. Overall, if blood pressure is too high, it can stimulate the vagus nerve reflexively, like ephedrine, and slow the heart rate. It can also cause tissues to not get enough blood, which can cause hypoxia and acidosis [28].

An open label randomized trial, they examined the prophylactic use of both NE and EP in CS delivery, they found no significant difference in hemodynamic parameters (HR, BP, and cardiac output) and number of recure vasopressors medication. In this study the authors used a fixed-rate infusion which is a different approach than used by [16] which used a computer-controlled closed-loop feedback system to administer and titrate the vasopressors with CO as the primary outcome, and in the current study which used an intermittent bolus injection for controlling hypotension. These different led to different doses used for various studies.

Also, in the [16, 22] an estimate of a potency ratio of 20:1 was used , while they used potency ratio of 2:1. Last a study defined hypotension as the requirement for rescue bolus intervention, which is different from our study >20% reduction from the initial value of MAP. Ephedrine is a drug that is often used to prevent and treat low blood pressure after lumbar anesthesia for a cesarean section. It can relax smooth bronchial muscles and stimulate the central nervous system, which causes the coronary arteries and cerebrovascular system to expand and the cardiac output to rise [22].

## Conclusion

In spinal anesthesia for CS devilries, NE is an efficient and secure vasopressor that prevents postanesthetic hypotension. Norepinephine and ephirdine both cause hypotensive episodes, but Norepinephine does so less frequently. Norephedrine has a more favorable hemodynamic effect on pregnant women than ephedrine. Less incidence of nausea in Norephedrine compared to Ephedrine.

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