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Hypotension Induced by Spinal Anesthesia in Cesarean Delivery: What ‘s the Difference between Ephedrine Vs Phenylephrine?

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ABSTRACT

Aims: to revisited the comparison beneficiary but unwanted hypotension effect due of application two different vasopressors namely phenylephrine versus ephedrine in cesarean delivery under spinal anesthesia.
Discussion: Elective cesarean sections are so commonly performed under spinal anesthesia. Unfortunately, this procedure often leads to hypotension, which may adversely jeopardize maternal and fetal outcomes. Immediate post spinal anesthesia hypotension is basically elucidated as reduction of normal blood pressure, estimated 80–90% below its baseline value. Various strategies have been implemented to reduce the incidence of spinal anesthesia-induced hypotension, including the immediate administration of vasopressors such as phenylephrine and or ephedrine, aimed for preventing and treating hypotension. Clinically, both phenylephrine and ephedrine were proven effective in protecting normal maternal hemodynamic balance. Newborns benefited more from the application of phenylephrine in elective cesarean delivery, compared to those who receive ephedrine, but unfortunately not in unscheduled emergency cesarean delivery or in vulnerable parturient with pre-eclampsia. More in depth clinical study should be conducted to obtain more conclusive results.

Keywords: hemodynamic, vasopressors, management, elective cesarean delivery

1. INTRODUCTION

Hypotension, or settled low blood pressure, is a common side effect of spinal anesthesia [Ghidini, et al., 2023]. Intraoperative hypotension immediately after spinal anesthesia conducted for Caesarean section is associated with maternal morbidity and mortality [Zwane, et al., 2018] and also to the neonatal outcomes [Knigin, et al., 2020]. Even though it can pose dangerous risks both for the maternal and neonatal but actually it is manageable [Park & Choi, 2024].

Hypotension actually is a recurrent side effect of spinal anesthesia, occurring in the range of incidence varies in divergent studies, from 7.4% to 74.1% of cases [Šklebar, et al., 2019].

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Several factors, including maternal characteristics [Santoso, et al., 2024] and anesthetic techniques [Bhat, et al., 2024], can affect the risk of occurring hypotension. Basically, it occurs due to a decrease in systemic vascular resistance and/or cardiac output, often exacerbated by the supine position during procedures like cesarean sections [Patel & Ninanve, 2024]. The physiological changes that occur during pregnancy necessitate modifications to anesthesia and analgesia procedures to provide safe and efficient care for the expectant patient [Patel & Ninave, 2024). While mild hypotension may be managed with volume expansion, e.g., infusion of fluids to increase effective blood volume [Chooi, et al., 2017]; but on the other hand severe or expeditiously worsening condition mandate aggressive treatment with vasopressors like phenylephrine or ephedrine, and in extreme cases, epinephrine [Biricik, et al., 2020]. The aim of this review is to compare the effectivity of ephedrine versus norepinephrine in treating anesthesia-induced hypotension in c- sectio patients.

2. EPHEDRINE

Ephedra or Ma huang species of plants are widely used for their medicinal properties. Ma-huang had variable effects on blood pressure and increased heart rate in healthy, normotensive adults [White, et al., 1997]. Polysaccharides are macromolecular components in Ephedra plants. At present time, the foremost polysaccharides secluded from Ephedra are polysaccharides A, B, C, D, and E, and hyperbranched acidic polysaccharides (ESP-B4) [Tang, et al., 2023]. The main functioning constituent in the Ephedra species is ephedrine [González-Juárez, et al., 2020]. Ephedrine is a phenethylamine alkaloid. which, as naturally occurring ephedrine alkaloids, possesses two chiral center carbon atoms and has four stereoisomers, (1R,2S)–(−)–ephedrine, (1S,2R)–(+)–ephedrine, (1S,2S)–(+)–pseudoephedrine, and (1R,2R)–(−)–pseudoephedrine [Segawa, et al., 2021]. Chemically, it's a substituted amphetamine derivative with a hydroxyl group (-OH) and an amino group, making it similar to epinephrine and methamphetamine.

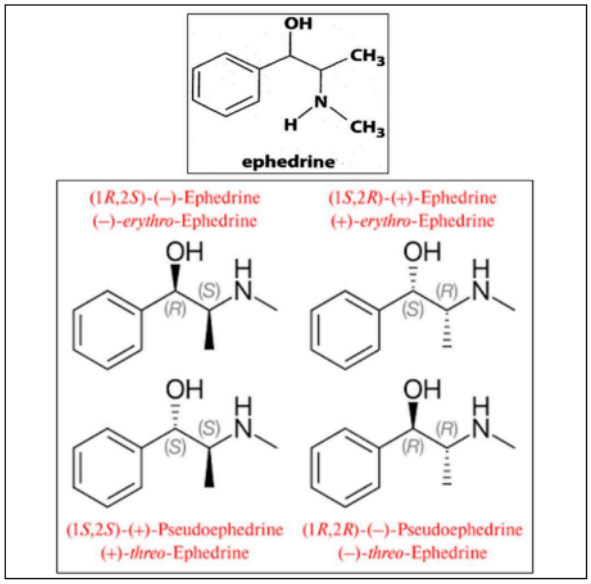

Fig. 1. Chemical structure of Ephedrine and its four stereoisomers

Ephedrine, a stereoisomer to the widely-known pseudoephedrine, is a sympathomimetic amine with unique effects due to its indirect mechanism than other sympathomimetic agents like pseudoephedrine and phenylephrine [Mandal, et al., 2024]. Ephedrine, a synthetic noncatecholamine agonist at α, β1, and β2 receptors, acts as both a direct and indirect sympathomimetic [Statler, et al., 2023]. Its primary method of action is secondarily accomplished by disrupting neuronal traffic of norepinephrine reuptake and displacing more norepinephrine from storage vesicles in the nerve cells [National Center for Biotechnology Information, 2025]. This mode of action permits norepinephrine to dwell sufficiently and extendedly in the synapse cleft region to bind postsynaptic alpha and beta receptors. This prolonged interaction is crucial for norepinephrine ability to effectively modulate various brain functions like arousal, attention, and mood [Maity, et al., 2022].

Ephedrine's indirect mechanism results in heart's activated chronotropic effect, marked by sustained or even increased heart rate [Kitaura, et al., 2019] as a consequences of the norepinephrine's ability to bind alpha and beta receptors [Gordan, et al., 2015], whereas more direct sympathomimetic like phenylephrine results in reflex bradycardia, in higher doses, it can trigger dangerous and extreme reflex bradycardia or even asystole [Horowitz, et al., 2023].

Intravenous ephedrine administration leads to several hemodynamics changes [Wang, et al., 2025] which consists of

1. increases in heart rate which sometime can also cause or worsen tachycardia [Abe, et al., 2023], as in case of propofol anesthesia which actually augments the pressor responses to i.v. ephedrine [Kanaya, et al., 2002],

2. increases in systolic and diastolic blood pressure [Ali Elnabtity & Selim, 2018]. Prophylactic ephedrine significantly attenuated the decrease in blood pressure and heart rate during induction of anesthesia with fentanyl and propofol [Shin, et al., 2002].

3. Mean arterial pressure [Ali Elnabtity & Selim, 2018] and cardiac output [Mon et al., 2017]. A study conducted by Uemura et al which aimed to determine whether aging would reduce the pressor effect of ephedrine on hypotension during general anesthesia. Those researchers found out that the administration of ephedrine significantly increased MAP and CO; however, no significant correlation with age was observed in patients aged > 45 years. These findings suggest that ephedrine is effective for the correction of hypotension during general anesthesia, even in elderly patients [Uemura, et al., 2023], and

4. coronary artery blood flow [Ishikawa, et al., 2011]. Ishikawa et al., reported co-administration of ephedrine prevents reductions in cardiac output and systemic oxygen delivery secondary to lung compression maneuvers during one-lung ventilation, without reducing arterial oxygenation

Ephedrine is therefore useful during general or regional anesthesia to treat hypotension [Statler, et al., 2023]. Worthy to note that the indirect effect is most profound on arterial blood pressure [Ali Elnabtity & Selim, 2018; Shin, et al., 2002], while on the other hand the direct vasoconstriction action roles on vessels, especially more on the venous system, just as in the case of their vasoconstrictive action on the nasal mucosa, ephedrine (and also pseudoephedrine) are highly efficient amines for relief of nasal congestion [Laccourreye, et al., 2015]. And in systemic context, therefore, the administration of ephedrine is effective in elevating central venous pressure when the patient is challenged with fluids [El-Mekawy, et al., 2012].

Clinically, stimulation of α-1 adrenergic smooth muscle receptors within vasculature wall results in an increase in systemic vascular resistance [Trammel & Sapra, 2023] with the consequences of elevation in blood pressure, either systolic or both with diastolic [Magder, 2018]. Stimulation of β-1 receptors [Alhayek & Preuss, 2023] by norepinephrine and ephedrine directly elevates cardiac chronotropic and inotropic [lin, et al., 2022]. eventually, β-2 adrenergic receptor stimulation in the lungs outturn in bronchodilation [Abosamak & Shahin, 2023] with ephedrine administration, which widens the airways and eases breathing, though it is not as pronounced as its cardiovascular effects [Statler, et al., 2023].

3. PHENYLEPHRINE

Phenylephrine is a small-molecule compound of organic substance with the molecular formula C9H13NO2 and a molecular weight of 167.205 g/mol. It is a highly hydrophilic compound, with an experimental log P of -0.3. Phenylephrine's chemical structure is that of a substituted phenethylamine, specifically (R)-β,3-dihydroxy-N-methylphenethylamine. It is closely related to epinephrine, differing only by the absence of one hydroxyl group on the phenyl ring. Phenylephrine is a chiral compound, and the (R)-stereoisomer is the form used in medications. The molecule contains an aromatic ring, a hydroxyl group (-OH), and an amine group (-NH2) [National Center for Biotechnology Information, 2025].

Phenylephrine incipiently performs as a relatively selective α-1 adrenergic receptor agonist [Richards, et al., 2023] and displays negligible beta-adrenergic activity [Torp, et al., 2001] or inotropic effect [Varma, et al., 2003] and therefore does not increase contractility [Kalmar, et al., 2018]. Alpha-1 agonists are a group of medications applied in the stewardship of many diseases, including hypotension as in the case of post-spinal hypotension in pre-eclamptic patients undergoing caesarean section [Mohta et al., 2023], hypoperfusion [Meng, et al., 2024], circulatory shock [Hollenberg, 2011], septic shock [Hawn, et al., 2021; Bonfiglio, et al., 1990], cardiac arrest [Cope, et al., 1997], pulmonary arrest [Joyce, et al., 1983] and also other lower acuity conditions such happen in accommodative system of the eyes [Esteve-Taboada, et al., 2016].

Consequently, the medication is an optimal choice for raising mean arterial pressure [Etania, et al., 2025] by inducing vasoconstriction in both veins and arteries [Højlund, 2024] and enhancing cardiac preload [Kalmar, et al., 2018, Valks, et al., 2002] without exerting significant effects on cardiac myocytes [Valks, et al., 2003]. The US Food and Drug Administration (FDA) has approved intravenous phenylephrine hydrochloride to elevate blood pressure in adults experiencing clinically significant hypotension, primarily attributed to vasodilation, in situations such as septic shock or anesthesia [The US Food and Drug Administration (FDA)].

Phenylephrine HCl is also an over-the-counter (OTC) medication in ophthalmic formulations to facilitate mydriasis and vasoconstriction of conjunctival blood vessels. Furthermore, this medication is administered intranasally to treat uncomplicated nasal congestion and is an OTC additive to topical hemorrhoid medications. [Richards, et al., 2023]

4. WHICH ONE IS PREFERRABLE FOR C SECTIO?

In the past 20 years, many studies have differentiated the effect of phenylephrine with ephedrine to prevent or treat hypotension in elective or emergency cesarean delivery and parturient with pre-eclampsia [Etania et al., 2025; Park & Choi, 2024; Santoso, et al., 2024; Ghidini, et al., 2023; Xu, et al., 2018]. These studies generally indicate that both drugs are effective in preventing or treating hypotension, but they have different characteristics and potential benefits or drawbacks.

During those past decade, phenylephrine, a primarily alpha-adrenergic agonist, has been the preferred vasopressor for cesarean sections [Park, et al., 2024]. Phenylephrine, a potent selective α-1 adrenergic agonist with minimal to no β-agonist activity [Richards, et al., 2023]. the use of phenylephrine is recommended and an optimal choice for raising mean arterial pressure by inducing vasoconstriction in both veins and arteries and enhancing cardiac preload without exerting significant effects on cardiac myocytes. The US Food and Drug Administration (FDA) has approved intravenous phenylephrine hydrochloride to elevate blood pressure in adults experiencing clinically significant hypotension, primarily attributed to vasodilation, in situations such as septic shock or anesthesia [US FDA, 2012]. Phenylephrine has earned popularity and preference owing to its advantages over ephedrine, particularly in preventing and treating spinal hypotension during anesthesia.

While both drugs can raise blood pressure, phenylephrine is favored for its more targeted vasoconstrictive action [Højlund, 2024] and reduced impact on beta-adrenergic receptors [Torp, et al., 2001], which can lead to fewer side effects [Xu, et al., 2018]. In managing maternal hypotension during spinal anesthesia for cesarean delivery, both phenylephrine and ephedrine are used, but they have different effects on neonates. Phenylephrine, a pure alpha-adrenergic agonist, is associated with higher umbilical artery pH values, potentially indicating less fetal acidosis, but it may also cause maternal bradycardia [Cooper, et al., 2002]. Ephedrine, a mixed alpha- and beta-adrenergic agonist, can cause fetal tachycardia and acidosis due to its placental crossing and stimulation of fetal beta-adrenergic receptors [Landau, et al., 2011].

Closed noninvasive monitoring during cesarean section (C-section) can help prevent hypotension [Vasile, et al., 2023; Illies, et al., 2012] and actually have the potential to revolutionize patient monitoring [Fortin, et al., 2021]. Technique such as continuous, non-invasive blood pressure monitoring systems [Fortin, et al., 2021], like the CNAP device, are more effective at detecting rapid blood pressure changes and hypotension compared to traditional intermittent methods [Yamada, et al., 2018]. This allows for timely intervention with vasopressors and fluids, potentially preventing or mitigating hypotensive episodes immediately and prevent a more catastrophe condition.

4. CONCLUSION

Ephedrine and phenylephrine, while crucial for managing hypotension during cesarean sections, have limitations that include potential side effects on both the mother and the fetus, and the need for careful titration to avoid complications. These limitations stem from the drugs' mechanisms of action and the unique physiological considerations of pregnancy.

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DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative AI technologies such as large language models (chatgpt, copilot, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

"Authors have declared that no competing interests exist.".

AUTHORS' CONTRIBUTIONS

'Author RHS' solely designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript, managed the literature searches"

CONSENT (WHERE EVER APPLICABLE)

Not needed

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

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