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Preoperative Oral Midodrine versus Intraoperative Intravenous Norepinephrine in Preventing Post- Spinal Anesthesia Hypotension: Review Article

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ABSTRACT

Background: Spinal anesthesia (SA)–induced hypotension is a frequent and potentially serious complication during Cesarean delivery, affecting up to 80–90% of parturients and contributing to maternal symptoms (Nausea & dizziness) and adverse fetal outcomes (Acidosis & bradycardia). While, preload and co-loading strategies offer limited benefit, vasopressor prophylaxis remains the cornerstone of management. Oral midodrine—a prodrug α_1-adrenergic agonist—and intravenous norepinephrine—a potent α-agonist with mild β_1 activity—have emerged as promising agents to stabilize systemic vascular resistance and maintain arterial pressure.

Objective: This article aimed to critically review and compare the efficacy, safety, and practical considerations of preoperative oral midodrine versus intraoperative continuous norepinephrine infusion for the prevention of SA–mediated hypotension in CSs.

Methods: We searched PubMed, Google Scholar, and Science Direct for Midodrine, Norepinephrine, Spinal anaesthesia, Hypotension, Cesarean section, Vasopressor prophylaxis. Only the thorough investigation, from 1994 to 2019, was taken into account. The writers evaluated relevant literature references as well. Documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts were excluded.

Conclusions: Both preoperative midodrine (5–10 mg orally ≥60 minutes before block) and low-dose norepinephrine infusions (2–8 μg/min) significantly reduce the incidence and severity of post-spinal hypotension. Midodrine's ease of administration and sustained effect suit settings without infusion pumps, while norepinephrine allows rapid, dynamic titration for tighter blood pressure (BP) control. Future large-scale trials are warranted to standardize dosing, validate fetal safety, and integrate these strategies into enhanced recovery protocols.

Keywords: Midodrine, Norepinephrine, Spinal anaesthesia, Hypotension, Cesarean section, Vasopressor prophylaxis.

INTRODUCTION

The use of neuraxial blockades in numerous surgical procedures, such as cesarean sections (CSs), as SA, can result in pharmacological sympathectomy, which can produce severe hypotension and potentially injure the patient. This SA-induced hypotension must be prevented at all costs. Nowadays, intravenous fluid pre-hydration, sympathomimetic medications, and physical measures including posture and leg compression are used to avoid hypotension [(1)].

Vascular tone and arterial pressure frequently drop noticeably as a result of the sympathetic blockage that SA causes. Both norepinephrine, an intravenous vasopressor with strong α-adrenergic effects and little β-activity, and midodrine, an oral α_1-adrenergic agonist that increases systemic vascular resistance, have been suggested as preventative measures to combat this. While a low-dose norepinephrine infusion initiated at the time of anesthesia may dynamically titrate peripheral resistance and preserve hemodynamic stability, midodrine administered before the onset of the block is thought to strengthen baseline vascular tone, thereby lessening the severity of post-spinal hypotension. Volume loading alone may not be as efficient in reducing BP fluctuations as these techniques, which address the main pathways of sympathectomy-induced vasodilation [(2)].

In this review, we aim to summarize and review current literature regarding the use of preoperative oral midodrine with intraoperative intravenous noradrenaline in reducing the risk of SA-induced hypotension during CS.

SPINAL ANESTHESIA

Proper placement and knowledge of neuraxial anatomy are necessary for SA administration. Getting the right amount of anesthetic into the intrathecal (subarachnoid) region is the aim [(3)].

Understanding dermatomal anatomy is critical for determining the amount of blockage in target tissues. For lower abdominal CSs, the incision is often performed below the T10 dermatome. However, covering of up to T7 dermatomes is essential to avoid discomfort or suffering from peritoneal pulling, which is notably noticeable with uterine manipulation. Patients report "pulling on their inside." Some dermatomal landmarks include: C8: 5th finger; T4: nipple; T7: xiphoid process; and T10: umbilicus [(4)].

Preparation: The induction of neuraxial anesthesia should be preceded by a comprehensive physical examination and history. The patient's name, the proposed operation, any allergies, permission, and a vocal declaration of coagulation status should all be confirmed during a procedural time-out. Select the proper LA. Which LA is appropriate? Isobaric,

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hyperbaric, or hypobaric pretreatment is required. The suggested length of the surgical intervention and the blockade duration should coincide. This is where additives come into play. In order to extend and/or enhance the quality of the block, epinephrine may be added [5].

LAs that are frequently used include lidocaine 5%, which acts quickly (within three to five mins) and produces anesthesia for 1-1.5hrs; buprevacaine 0.5%, which is a commonly used agent with an onset of five- to eight mins and a duration of 90-150 mins; tetracaine 0.5%; mepivacaine 2%; ropivacaine 0.75%; levobupivacaine 0.5%; and chloroprocaine 3%, each of which has a range of onset times and durations that are appropriate for certain clinical applications [6].

Positioning:

SA is administered in 3 different positions: prone, sitting, and lateral decubitus:

1) Lateral Decubitus: reduces the need for a positioning helper and enables the anesthesiologist to deliver more sedative. (A patient should never be oversedated). The back of the patient is positioned parallel to the OR table's side. In the fetal position, the neck is bent forward and the thighs are flexed up. It is important to arrange patients so they can benefit from the spinal LA [7].

2) Sitting: used for sacral and lumbar anesthesia (perineal, urological). If the right amount of LA is given and the patient is positioned as soon as possible to maximize the distribution of LA, higher levels of anesthesia can be achieved. Determine the landmarks of anatomy. Obese people or those with abnormal spinal curvatures may find this difficult. Place the patient on a table in front of them, with their feet cushioned and down, or have them sit up straight with their head flexed and their arms embracing a pillow. Verify that the patient is not only bending forward [7].

3) Prone: For surgical operations (such as rectal, perineal, or lumbar procedures), the patient is placed in the prone position. Hypobaric LAs are produced. In order to decrease lumbar lordosis, the patient arranges themselves; a paramedian technique is frequently employed [7].

Projection and Puncture: With the stylet in place, insert the spinal needle (via the introducer, if appropriate), making that the bevel is tilted slightly cephalad and oriented laterally, keeping the stylet in the midline. Proceed gradually until you feel more resistance when you reach the ligamentum flavum, then less resistance when you enter the epidural space, and finally less resistance when you puncture the dura. When you withdraw the stylet, CSF should start to flow (give yourself four–five seconds if you're using a twenty five-gauge needle). Withdraw about 1 cm and re-advance more cephalad, maintaining midline, if bone is touched. Once the CSF is visible, immobilize the needle by pressing the back of your non-dominant hand against the patient and using your thumb and index finger to hold the hub. Then, securely fasten the LA syringe, aspirate softly to ensure intrathecal insertion, and inject slowly. Lastly, apply a sticking plaster to the puncture site and remove the needle, introducer, and syringe together [8].

Contraindications: Serious recognized contraindications exist for both spinal and epidural neuraxial anesthesia. Infection at the surgery site (risk of meningitis), excessive intracranial pressure (ICP), mainly from an intracranial mass, and the patient's lack of consent are the absolute contraindications. Relative contraindications are: Some relative contraindications include severe aortic and mitral stenosis, hypertrophic obstructive cardiomyopathy-induced left ventricular outflow obstruction, preexisting neurological conditions (particularly those that wax and wane, like multiple sclerosis), severe dehydration (hypovolemia), and the risk of hypotension, which is increased by factors such as hypovolemia, age over 40 to 50, emergency surgery, obesity, chronic alcohol use, and chronic hypertension [9].

Complications of SA

A) Meningitis: Following SA, meningitis, either bacterial or aseptic, may develop. The anesthesiologist's oral flora, patient illness, and contaminated spinal trays and medicine are among the sources of infection. Nonsteroidal anti-inflammatory medications, certain antibiotics, and radiography agents are examples of pharmaceuticals and chemicals that can cause meningitis. Additionally, it seems that underlying collagen, vascular, or rheumatologic diseases are linked to the incidence of hypersensitivity-type responses [10].

B) Vertebral canal hematoma: After SA, vertebral canal hematoma development is an uncommon yet deadly consequence. A few instances have identified subarachnoid hemorrhage as the source of neurologic impairments, despite the fact that the majority of spinal hematomata occur in the epidural space because of the large epidural venous plexus. Either a damaged vein or an injured artery may be the cause of the bleeding [10].

C) Spinal cord ischemia: A pial plexus and three longitudinal arteries—the anterior spinal artery and two posterior spinal arteries—make up the spinal cord's superficial vascular system. Numerous anastomoses shield the posterior chord from ischemia to a considerable extent. Because the core region of the anterior spinal cord depends on the anterior spinal artery, it is more vulnerable to ischemia. A vertebral canal hematoma compressing the arterial supply, adding vasoconstrictors to LAs, and persistent hypotension are some of the hypothesized causes of spinal cord ischemia resulting from spinal blockage [10].

D) Peripheral nerve injury: Injury to peripheral nerves may be an indirect consequence of SA. Normal defensive responses are momentarily eliminated by the sensory block caused by SA. As a result, proper placement, avoiding tight plaster casts, and monitoring distal circulation all require caution. Therefore, it is

essential that limbs rendered insensate by SA receive quality nursing care [10].

E) Total SA: Total SA (TSA) causes respiratory depression, cardiovascular impairment, and a loss of consciousness. This might be preceded by numbness, paresthesia, or weakening of the upper limb, shortness of breath and nausea or anxiety [10].

F) Cardiovascular collapse: Although it is an uncommon occurrence, cardiovascular collapse might happen following SA [11].

G) Nausea and vomiting: In addition to being upsetting for the patient, nausea and vomiting following SA can also make the surgeon's job more difficult. Hypotension, intrathecal additives, insufficient block, or high block are some of the ways that SA itself might result in intraoperative nausea and vomiting (IONV) or postoperative nausea and vomiting. Peak block height larger than T6, baseline HR of 60 beats per minute or higher, motion sickness history, and prior hypotension following spinal block are risk factors for IONV under spinal anaesthesia [11].

H) Shivering: Shivering can be brought on by spinal, epidural, and even general anesthesia. Given the variability of research, it is challenging to determine the incidence of shivering due to neuraxial block, however it is around 55% [11].

I) Post-dural puncture headache (PDPH): A serious side effect of neuraxial anesthesia, PDPH can happen after SA or when a dural puncture happens accidentally during epidural anesthesia. Due to their age, sex, and the frequent use of neuraxial blocks, obstetric patients are thought to be more susceptible to this syndrome [11].

J) Hypotension: Reliable spinal blocks have predictable negative effects, such as fetal acidosis, reduced uteroplacental blood flow, and maternal hypotension that causes nausea and vomiting. The most widely used definition of spinal-induced hypotension is a 20% drop from baseline BP, an incidence of 70–80% has been reported [11].

SA-INDUCED HYPOTENSION

90% of women may experience SA's primary drawback, maternal hypotension, which can result in dizziness, nausea, vomiting, fetal acidity, and in extreme situations, fetal bradycardia and cardiovascular collapse. Reduced systemic vascular resistance results in hypotension, which is made worse in parturients by compression of the inferior vena cava. This is somewhat offset by an increase in heart rate and stroke volume. There is debate regarding the optimal way to avoid hypotension during CS [12]. Pregnant women experience greater incidence and degrees of hypotension than non-obstetric patients, mostly due to aortocaval compression of the pregnant uterus and heightened sensitivity to LAs. Also, pregnant women show higher sympathetic than parasympathetic activity [13]. Although the degree of the ensuing sympathetic block varies greatly from patient to patient, the cardiovascular effects of SA are related to the degree of the accompanying sympathetic block [14].

Prevention of SA-induced hypotension

SA has long been researched for its ability to prevent and cure hypotension following Cesarean birth since it can have major effects on both the mother and the fetus. The effectiveness of crystalloid fluid loading has been questioned recently, despite its traditional

Effect of SA on the resistive and capacitive vascular systems

The sympathetic block that SA produces causes arterial and arteriolar vasodilation in the affected areas very quickly. This, in turn, causes a baroreflex to increase sympathetic arterial vascular tone in the non-blocked areas. In younger patients, these compensating mechanisms tend to work better. Additionally, the hemodynamic effects of SA cause a sympathetic block of the venous reservoir, which causes blood to pool in the lowermost capacitance veins. Vasopressors can mobilize the circulating blood volume, which can be affected by up to 20% of the pooling in the hepato-splanchnic area when the level of the sensory block is greater than or equivalent to T6[14].

Effect of SA on the cardiac system

Because SA causes a sympathetic imbalance in favor of the parasympathetic tone, it reduces BP and causes bradycardia. A disturbance of cardiovascular function might be the cause of this bradycardia/hypotension, or it could be seen as an adaptive response (Extending the diastole time to encourage ventricular filling). The aortic and carotid baroreceptors, together with the cardioinhibitory receptors of the Bezold–Jarisch reflex (BJR), are known to have a role in the physiological control of arterial BP [15]. Moderate hypovolemia causes the BJR's activity to decrease, while simultaneously stimulating the baroreflex, which raises arterial BP. A rapid decline in venous return in cases of acute hypovolemia, such as extensive bleeding, causes a paradoxical activation of the BJR, resulting in bradycardia and persistent hypotension. The latter may be an adaptive strategy to maintain diastolic filling time. Bradycardia occurs in around 13% of non-obstetrical patients during SA, but as long as remedial action is performed right away, there are usually no serious repercussions [16].

But, since severe bradycardia can quickly lead to asystole, bradycardia brought on by SA should always be regarded as a warning indication of an imminent hemodynamic collapse. There is a biphasic impact of SA on cardiac output: It first rises as a result of arterial vasodilatation, which lowers afterload, reaching a maximum after around seven minutes, and then falls as a result of a drop in preload. 15% to 50% of patients have a drop in arterial BP, which can be attributed in part to this decrease in cardiac output. Age-related alterations (Diastolic relaxation & systolic function) might exacerbate the decline in cardiac output in the elderly [16].

usage. Large crystalloid volumes may cause disruptions to the glycocalyx, and some obstetric patients may exhibit higher cardiac output after spinal cord injury, which calls into doubt the viability of preload techniques. Colloid administration , or colloid-crystalloid combinations, can further reduce the incidence or severity of hypotension, but they carry a greater risk of allergy. Rapid co-loading of 500–1500 mL crystalloids at the time of block induction has demonstrated minor benefits over preloading [(11)]. In order to attain the best possible BP control during SA for CS, co-loading with 1000–2000 mL of crystalloids and a continuous hemodynamic infusion medication that regulates blood vessel tone can greatly enhance patient BP control and avoid the onset of an acute BP drop [(2)].

NORADRENALINE

The components of noradrenaline or norepinephrine are an ethylamine side chain, which has a hydroxyl group attached in the benzylic position, and a catecholamine, which is a benzine ring with two adjacent hydroxyl groups in the meta-para position. A hydrogen atom takes the place of the methyl group in norepinephrine, in contrast to epinephrine, which has a methyl group attached to the nitrogen [(2)].

BIOCHEMICAL MECHANISMS

➢ *Biosynthesis*

Tyrosine is converted into norepinephrine by a sequence of enzymatic processes in the sympathetic nervous system's postganglionic neurons and adrenal medulla. Dopamine β-monooxygenase converts dopamine to norepinephrine mostly inside neurotransmitter vesicles, whereas tyrosine is primarily converted to dopamine in the cytoplasm [(17)].

➢ *Removal and Metabolism*

The amount of NE in the junctional cleft will drop if the neuron ceases to release it, and NE will exit the receptor. Numerous processes are involved in the removal of norepinephrine from the postjunctional receptor and the intercellular (junctional) gap. These processes include metabolization in the extracellular space, surrounding tissue, or reuptake into the nerve terminal [(18)].

➢ *Mechanism of Action*

Norepinephrine is a sympathetic amine produced from tyrosine. It has the same structure as epinephrine but lacks a methyl group on the nitrogen atom. The difference renders it largely agonistic at α1 and β1 receptors, with little to no β2 or α2 action [(18)]. At modest dosages (less than 2 mcg/min), β1 effects may be more evident, perhaps increasing CO levels. Though, at dosages over 3 mcg/min, the alpha1 effects may predominate. Activation of the α1 receptor causes vasoconstriction and a dose-dependent increase in systemic vascular resistance. The venue to arterial activity ratio is almost equal. The action begins within 1-2 minutes. The activity will last between 5 and 10 minutes. Half-life: 3 minutes [(18)].

➢ *Administration*

Norepinephrine is usually administered by continuous infusion because of its comparatively short half-life of 2.5 minutes. To prevent oxidation and consequent loss of medication efficacy, the FDA advises diluting concentrated norepinephrine with solutions including dextrose prior to infusion. The FDA expressly advises against use saline as the only diluent. Starting the infusion at 8-12mcg per minute and titrating to the required pressure is a typical method. Approximately 2-4 mcg per minute is the typical maintenance dosage. Tubing used for norepinephrine infusions should ideally be kept apart from blood products [(19)].

➢ *Adverse Effects*

Alpha1 receptor activation is intimately related to the most frequent negative effects of norepinephrine. In other words, excessive vasoconstriction can lead to decreased end-organ perfusion, which is mainly caused by norepinephrine infusions without proper treatment of hypovolemia. This can be harmful because the majority of patients who need norepinephrine infusions already have poor oxygen delivery or utilization [(19)].

Reflex bradycardia can be caused by vasoconstriction owing to α1 activation through the baroreceptor reflex, which is often not compensated for by β1 activity. The net effect is that, in spite of beta1 agonism, CO may drop or at most remain unchanged. At the same time, the rise in systemic vascular resistance causes the heart to work harder by raising afterload, which raises the oxygen demand on the heart. These events make it difficult to determine if norepinephrine is beneficial for cardiogenic shock, but it is taken into consideration in some situations. When norepinephrine is administered, pulmonary vascular resistance may rise, which might have detrimental effects on people with pulmonary hypertension. Drugs that undergo hepatic metabolism may temporarily rise as a result of decreased hepatic blood flow (Due to α-mediated vasoconstriction) [(20)].

➢ *Norepinephrine in SA-Induced Hypotension*

Recently, norepinephrine has been proposed as a potential substitute for phenylephrine in the maintenance of BP during SA for CS. However, it has been suggested that before it can be deemed appropriate for standard clinical practice, further information regarding its application in this setting should be gathered [(21)]. Prior studies on the administration of norepinephrine during SA for CS have detailed intermittent boluses, fixed-rate infusion, and computer-controlled infusion. There is no prior description of the administration of manually titrated norepinephrine infusions to obstetric patients. Other vasopressors, such phenylephrine, are frequently administered in this manner [(22)].

MIDODRINE

A peripherally acting α-receptor agonist, midodrine comes in pills containing 2.5 mg and 5 mg.

Both α1-and α2-receptors are not particularly affected by it. However, α1-receptors are selectively stimulated by its active metabolite, desglymidodrine. In a dose-dependent fashion, it raises BP somewhat when standing and while reclining. Other pharmacodynamic effects include lowering blood volume and circulating plasma, increasing venous tone and atrial natriuretic peptide release, and raising peripheral vascular resistance [23].

- **Pharmacology of midodrine**

Midodrine does not directly activate the central nervous system because of its limited blood-brain barrier penetration. It produces QT prolongation, lowers heart rate and circulating noradrenaline levels through baroreceptor stimulation, and indirectly raises end-diastolic and stroke volumes while having little myocardial ß-adrenoreceptor action. It doesn't significantly affect endocrine or metabolic processes. Insulin, uric acid, and serum lipids are unaffected. Additionally, it has no known impact on immunological, coagulation, renal, or pulmonary function. Pregnancy-related administration of it has been done safely [24]. Only four percent of a single dosage of midodrine is eliminated unaltered in the liver, where it is extensively metabolized by cytochrome P450 isoforms CYP2D6 and CYP1A2. The main way that midodrine and desglymidodrine are excreted is through the urine. The elimination half-life of desglymidodrine can be shortened to 90 mins by hemodialysis. The elimination half-life may reach ten hours in end-stage chronic renal disease [23].

- **Adverse effects**

The α-agonist characteristics of midodrine are linked to common side effects. The most commonly reported side effects include pilomotor reactions (Piloerection & scalp pruritus), cardiovascular effects (Supine hypertension & bradycardia), gastrointestinal and genitourinary complaints (Nausea, abdominal pain, urinary retention & dysuria), and central nervous system effects (Paraesthesia & taste and smell disturbance). These side effects are usually modest and dose-dependent, however many people may have one or more of them. Midodrine usage has been linked in a few case reports to takotsubo cardiomyopathy, vascular ischaemia, myoclonic seizures, intracerebral hemorrhage, reversible cerebral vasoconstriction syndrome, and ileus [25]. The most frequent side effect of intravenous vasopressor weaning agents in critical care settings is reflex bradycardia, which is proportionate to the amount of midodrine. Concurrent prescription of antiarrhythmics, ß-blockers, antipsychotics, monoamine oxidase inhibitors, tricyclic antidepressants metabolized by cytochrome CYP2D6, ranitidine, metformin, and procainamide may result in drug interactions because these medications compete with desglymidodrine at acute tubular secretion sites in the kidney [23].

- **Midodrine in SA-induced hypotension**

Midodrine hydrochloride is a prodrug that acts as a direct α1-adrenoceptor agonist. Its active metabolite, desglymidodrine, causes vasoconstriction in the arteries and veins. The overall outcome is an increase in both systolic BP (SBP) and vascular tone. Cardiac β-receptors remain unaffected, and there is no major blood-brain barrier penetration. In healthy people, a 10 mg oral dosage can increase BP by 10-30 mmHg in one hour and remain raised for some time. Midodrine has a high oral bioavailability and a generally benign profile, with few central nervous system adverse effects [26].

Numerous hypotensive syndromes, including orthostatic hypotension, weaning patients off IV vasopressors, lowering the frequency of hypotension during dialysis, and raising the SBP following dialysis, have all been successfully prevented with its help. Vasopressors with different adrenergic activities, such as ephedrine, phenylephrine, and norepinephrine, are effective in preventing and treating hypotension following SA. Ephedrine is an alpha and beta-adrenergic agonist that raises myocardial oxygen consumption and heart rate, which can have negative cardiovascular consequences [26].

Pure direct alpha-1 receptor agonist phenylephrine does not directly affect the heart rate, while norepinephrine, a strong α-adrenergic receptor agonist with a low level of β-adrenergic receptor activity, has a slight chronotropic impact but is just as effective as phenylephrine in vasopressors [23]. The use of alpha-agonists to treat hypotension caused by SA has been thoroughly studied in obstetrics. The current consensus favors phenylephrine over ephedrine as the preferred vasopressor agent because of its efficacy and positive impact on fetal acid-base balance and umbilical pH [26].

In order to shorten the time needed for IV vasopressor administration and enable faster hospital and critical care unit discharge, oral midodrine has been administered as an adjuvant to routine therapy [23].Previous studies have demonstrated that midodrine may also be utilized as a preventative measure against orthostatic hypotension. They discovered that administering ten mg of midodrine three times a day raised standing SBP by twenty-two mmHg when compared to a placebo [28]. When compared to a placebo, **Jans *et al.*** [29] found that an oral 5-mg midodrine prophylactic usage did not substantially lower the prevalence of orthostatic hypotension during early postoperative mobility. Furthermore, as **Levine *et al.*** [30] described that the use of midodrine in the ICU has decreased the length of stay in the ICU and early weaning from IV vasopressors. **Lal *et al.*** [31] employed midodrine in the early stages of sepsis and discovered that it might shorten the duration of stay in the ICU and lessen the requirement for norepinephrine.

CONCLUSION

Both preoperative midodrine (5–10 mg orally ≥ 60 minutes before block) and low-dose norepinephrine infusions (2–8 μg/min) significantly reduced the incidence and severity of post-spinal hypotension. Midodrine's ease of administration and sustained effect suit settings without infusion pumps, while norepinephrine allows rapid, dynamic titration for tighter BP control. Future large-scale trials are warranted to standardize dosing, validate fetal safety, and integrate these strategies into enhanced recovery protocols.

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REFERENCES

1. **Alseoudy M, Nasr M, Abdelsalam T (2022):** Efficacy of Preoperative Oral Midodrine in Preventing Hypotension After Spinal Anesthesia in Young Adults: A Randomized Controlled Trial. Anesth Analg., 135 (5): 1089–1096.
2. **Nadella H, Islam A, Ina E *et al.* (2024):** The Management of Spinal and Epidural Anesthesia-Related Hypotension in the United States During Cesarean Childbirth. Cureus, 16 (3): e56340. https://doi.org/10.7759/cureus.56340.
3. **Hermanns H, Bos E, van Zuylen M *et al.* (2022):** The options for neuraxial drug administration. CNS Drugs, 36 (8): 877–896.
4. **Plaat F, Stanford S, Lucas D *et al.* (2022):** Prevention and management of intra-operative pain during caesarean section under neuraxial anaesthesia: A technical and interpersonal approach. Anaesthesia, 77 (5): 588–597.
5. **Imbelloni L, Gouveia M, Ghorayeb N *et al.* (2021):** Spinal anesthesia: Much more than single shot of hyperbaric bupivacaine. Int J Anaesth Anesthesiol., 8: 122. DOI: 10.23937/2377-4630/1410122
6. **Kolli S, Oweidat A (2025):** Pharmacology of Local and Neuraxial Anesthetics. In Basic Sciences in Anesthesia: Springer, Pp: 169–185. DOI:10.1007/978-3-031-60203-0_9
7. **Olawin A, Das J (2025):** Spinal anesthesia. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK537299/.
8. **Martinello C, Williams M, Mhyre J (2023):** Regional Anesthesia and Analgesia for Cesarean Delivery. In: Regional Anesthesia and Acute Pain Medicine, Pp: 399. https://doi.org/10.1093/med/9780197518519.003.0035.
9. **Shatri G, Singh, A. (2025):** Thoracic Segmental Spinal Anesthesia. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK572087/
10. **Waters J (2022):** Neurologic Complications of Obstetric Anesthesia. Continuum, 28 (1): 162–179.
11. **Pozza D, Tavares I, Cruz C *et al.* (2023):** Spinal Cord Injury and Complications Related to Neuraxial Anaesthesia Procedures: A Systematic Review. International Journal of Molecular Sciences, 24 (5): 4665. https://doi.org/10.3390/ijms24054665.
12. **Fitzgerald J, Fedoruk K, Jadin S *et al.* (2020):** Prevention of hypotension after spinal anaesthesia for caesarean section: A systematic review and network meta-analysis of randomised controlled trials. Anaesthesia, 75 (1): 109–121.
13. **Okeagu C, Anandi P, Gennuso S *et al.* (2020):** Clinical Management of the Pregnant Patient Undergoing Non-Obstetric Surgery: Review of Guidelines. Best Practice & Research Clinical Anaesthesiology, 34 (2): 269-281.
14. **Olsen F, Dalla K, Ricksten S *et al.* (2023):** Fractional Spinal anesthesia and systemic hemodynamics in frail elderly hip fracture patients. F1000Res., 12: 210. doi: 10.12688/f1000research.130387.2.
15. **Ferré F, Martin C, Bosch L *et al.* (2020):** Control of Spinal anesthesia -induced hypotension in adults. Local Reg Anesth., 45 (22): 39–46.
16. **D'Amico F, Fominskiy E, Turi S *et al.* (2023):** Intraoperative hypotension and postoperative outcomes: A meta-analysis of randomised trials. Br J Anaesth., 12 (10): 53-58.
17. **Saboory E, Ghasemi M, Mehranfard N (2020):** Norepinephrine, neurodevelopment and behavior. Neurochem Int., 135: 104706. doi: 10.1016/j.neuint.2020.104706.
18. **Johnson B (2024):** Physiology of the Autonomic Nervous System. In: Basic Sciences in Anesthesia. Argalious M, Farag E, Sharma D (Eds.)., (2nd ed.), Springer, Pp: 355–364. https://link.springer.com/book/10.1007/978-3-031-60203-0.
19. **Murala S, Bollu P (2022):** Norepinephrine. In: Neurochemistry in Clinical Practice. Bollu P (Ed.), Springer International, Pp: 165–179. https://doi.org/10.1007/978-3-031-07897-2_9
20. **Stampfl M, DeBlieux P (2024):** A Clinical Review of Vasopressors in Emergency Medicine. The Journal of Emergency Medicine, 67 (1): 31–41.
21. **Tan H, Chen Y, Jiang Y *et al.* (2024):** Determination of ED90s of Phenylephrine and Norepinephrine Infusion for Prevention of Spinal anesthesia -Induced Hypotension in Patients with Preeclampsia During Cesarean Delivery. Drug Design, Development and Therapy, 18: 2813–2821.
22. **Mao J, Lin K, Liu X *et al.* (2025):** Effects of Prophylactic Infusion of Equivalent Doses of Norepinephrine and Phenylephrine in Preventing Spinal anesthesia -Induced Hypotension During Cesarean Delivery on Fetal and Maternal Outcomes: A Dual-Center, Non-Inferiority Controlled Trial. Drug Design, Development and Therapy, 19: 5143–5152.
23. **Costa-Pinto R, Yong Z, Yanase F *et al.* (2022):** A pilot, feasibility, randomised controlled trial of midodrine as adjunctive vasopressor for low-dose vasopressor-dependent hypotension in intensive care patients: The MAVERIC study. Journal of Critical Care, 67: 166–171.
24. **May C, Varnes B, Smetana K (2020):** Vasopressors 16. In: Pharmacology in Clinical Neurosciences. Springer Singapore, Pp: 917–925. DOI:10.1007/978-981-15-3591-8_16
25. **Ye X, Ling B, Wu J *et al.* (2020):** Case report: Severe myoclonus associated with oral midodrine treatment for hypotension. Medicine, 99 (40): e21533. doi: 10.1097/MD.0000000000021533.
26. **Park H, Choi W (2024):** Use of vasopressors to manage Spinal anesthesia -induced hypotension during cesarean delivery. Anesthesia and Pain Medicine, 19 (2): 85–93.

27. **Tchen S, Sullivan J (2020):** Clinical utility of midodrine and methylene blue as catecholamine-sparing agents in intensive care unit patients with shock. Journal of Critical Care, 57: 148–156.
28. **Palma J, Kaufmann H (2020):** Management of Orthostatic Hypotension. Continuum, 26 (1): 154–177.
29. **Jans Ø, Mehlsen J, Kjærsgaard-Andersen P *et al.* (2015):** Oral midodrine hydrochloride for prevention of orthostatic hypotension during early mobilization after hip arthroplasty. Anesthesiology, 123 (6): 1292–1300
30. **Levine A, Meyer M, Bittner E *et al.* (2013):** Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. Journal of Critical Care, 28 (5): 756–762.
31. **Lal A, Trivedi V, Rizvi M *et al.* (2021):** Oral midodrine administration during the first 24 hours of sepsis to reduce the need of vasoactive agents: Placebo-controlled feasibility clinical trial. Critical Care Explorations, 3 (5): e0382. doi: 10.1097/CCE.0000000000000382.