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Review

Use of vasopressors to manage spinal anesthesia-induced hypotension during cesarean delivery

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Cesarean sections are commonly performed under spinal anesthesia, which can lead to hypotension, adversely affecting maternal and fetal outcomes. Hypotension following spinal anesthesia is generally defined as a blood pressure of 80–90% below the baseline value. Various strategies have been implemented to reduce the incidence of spinal anesthesia-induced hypotension. The administration of vasopressors is a crucial method for preventing and treating hypotension. In the past decade, phenylephrine, a primarily alpha-adrenergic agonist, has been the preferred vasopressor for cesarean sections. Recently, norepinephrine, a potent alpha-agonist with modest beta-agonist activity, has gained popularity owing to its advantages over phenylephrine. Vasopressors can be administered via a bolus or continuous infusion. Although administering boluses alone is simpler in a clinical setting, continuous prophylactic infusion initiated immediately after spinal anesthesia is more effective in reducing the incidence of hypotension. Tailoring the infusion dose based on the patient's body weight and adjusting the rate in response to blood pressure changes, in addition to using a prophylactic or rescue bolus, helps reduce blood pressure variability during cesarean sections under spinal anesthesia until neonatal delivery.

Keywords: Anesthesia; Spinal; Cesarean section; Hypotension; Norepinephrine; Phenylephrine.

INTRODUCTION

Cesarean sections are commonly performed under spinal anesthesia, offering numerous benefits for the neonate and mother compared with general anesthesia, and it prevents the transfer of anesthetic drugs across the placenta, thereby protecting the baby. Spinal anesthesia also mitigates the risk of severe side effects associated with general anesthesia, such as maternal airway obstruction and aspiration pneumonia. However, the most common side effect of spinal anesthesia is hypotension, which occurs immediately following intrathecal injection. This condition can trigger nausea, vomiting, and dizziness in the mother and reduce blood flow to the placenta, potentially resulting in fetal acidosis and lower Apgar scores. Therefore, effectively addressing or preventing spinal-induced hypotension is crucial during cesarean sections performed under spinal anesthesia.

The management of spinal-induced hypotension includes the use of vasopressors coupled with techniques such as left lateral uterine displacement and intravenous (IV) fluid preloading or co-loading, as outlined in various guidelines [1-7]. This strategy is crucial, as hypotension arises from sympathetic vasomotor blockade in the spinal region. Ephedrine has conventionally been the preferred medication for man-

aging and preventing spinal hypotension. However, recent trends favor vasopressors such as phenylephrine and norepinephrine (NE) owing to their superior benefits [8-10]. Therefore, clinicians must stay abreast of the most effective medications for the management of spinal hypotension.

This study determined the management of hypotension during maternal spinal anesthesia for a cesarean section and explored various vasopressor options, infusion techniques, and dosing strategies. We relied on the "International Consensus Statement on the Management of Hypotension with Vasopressors during Cesarean section under spinal anesthesia," authored by Kinsella et al. [1] in 2018, as the foundational guideline for our analysis.

Definition of spinal anesthesia-induced hypotension

Although the definitions of spinal anesthesia-induced hypotension vary across studies, it is generally recognized as either an absolute systolic blood pressure (BP) between 80 and 100 mmHg, a decrease of 0–30% from the usual BP, or a combination of both [11]. Baseline BP is invariably measured before administering spinal anesthesia or upon admission to the labor and delivery unit using the average of three repeated measurements [9]. The most commonly used criteria for diagnosing spinal anesthesia-induced hypotension include a BP level less than 80% or 90% of the baseline value or a systolic BP of < 90 or 100 mmHg [11,12]. Consensus guidelines recommend preventing systolic arterial pressure from falling below 90% of the baseline value during a cesarean section. In patients with gestational hypertension or preeclampsia, although a definitive cutoff point has not yet been established, hypotension is typically defined as a BP level less than 80% of the baseline.

Consequences of spinal anesthesia-induced hypotension

The most common symptoms of hypotension are maternal nausea and vomiting. Sudden hypotension leads to decreased cerebral perfusion, causing transient ischemia of the brainstem, which activates the vomiting center [13-16]. Additionally, spinal anesthesia can decrease the splanchnic blood flow by approximately 20%, potentially triggering the release of emetogenic factors such as serotonin from the gastrointestinal tract, thereby inducing nausea and vomiting [17]. Moreover, the abrupt blockage of sympathetic nerves can induce gastrointestinal tract hyperactivity due to unexpected vagal stimulation [18]. When hypotension worsens or persists, symptoms such as dizziness or decreased consciousness may manifest.

Maternal hypotension after spinal anesthesia can cause severe acidosis in the neonate. Previous studies showed elevated levels of oxypurines and lipid peroxides in the umbilical vein, signaling ischemia-reperfusion injury, especially if hypotension persists for more than 2 min [19-21]. The duration of hypotension may outweigh its severity; transient decreases in BP of 30% or more do not affect neonatal Apgar scores or necessitate oxygen therapy [22]. However, hypotension that persists for more than 4 min has been associated with neurobehavioral changes in newborns 4–7 days after birth [23].

Noninvasive continuous blood pressure monitoring

Noninvasive BP measurements, typically obtained from various sites of the body, with the arm being the most common [24], involve the use of a standard automated digital oscillometric method. This method measures BP in cycles of at least 1 min and does not provide continuous real-time information. Such intermittent BP measurements may delay the treatment of hypotension during a cesarean section. Although invasive arterial monitoring can provide continuous arterial pressure, its routine application during cesarean sections may be limited owing to the occurrence of complications associated with invasive procedures, the relatively short duration of the surgery compared with other open abdominal surgeries, and the awake state of patients.

Recently developed noninvasive devices used to measure BP and monitor maternal hemodynamic variables such as cardiac index. Despite limited data, these noninvasive devices have shown potential for tracking responses to spinal anesthesia-induced sympathetic blockade and vasopressor administration without the need for invasive procedures in cesarean section [25-27]. For example, ClearSight™ (Edwards Lifesciences), a noninvasive continuous BP monitoring device using a finger cuff, has demonstrated acceptable accuracy and precision compared to that in invasive monitoring methods [28]. This device has been associated with a reduced incidence of hypotension and maternal nausea under spinal anesthesia [29]. Although the cost-effectiveness of these devices in cesarean sections warrants consideration, they can potentially decrease maternal blood pressure variability and enhance the quality of spinal anesthesia.

VASOPRESSOR AGENTS

Vasopressors primarily exert cardiovascular effects by acting on alpha-1-, beta-1-, and beta-2-adrenergic receptors. The commonly used vasopressors in clinical practice in Korea include ephedrine, phenylephrine, and NE (Table 1).

Ephedrine

Ephedrine, a mixed alpha- and beta-adrenergic agonist, primarily activates adrenergic receptors indirectly, although it has weak direct effects. Ephedrine typically enhances heart rate (HR) and contractility by stimulating cardiac beta-1-adrenergic receptors. Historically, ephedrine has emerged as the preferred vasopressor in obstetric anesthesia, supported by studies showcasing its efficacy in preserving uterine blood flow in a sheep model [30,31]. However, ephedrine exhibits a higher transplacental transfer rate compared to those in phenylephrine. The clinical use of higher ephedrine doses to mitigate hypotension has shown no improvement in neonatal acidosis and, in a few cases, has exacerbated it [32,33].

Phenylephrine

Phenylephrine acts as a potent direct alpha-1 receptor agonist without beta effects at clinical doses. In the last decade, it has become the preferred vasopressor for preventing and treating spinal hypotension, replacing ephedrine [8,32]. Phenylephrine increases systemic vascular resistance, systolic BP, and left ventricular afterload. However, it is associated with baroreceptor-mediated bradycardia, resulting in reduced maternal cardiac output [34]. Stewart et al. [35] observed dose-dependent reductions in maternal HR and cardiac output, measured using a suprasternal Doppler, when comparing three different infusion regimens (25, 50, and 100 μg/min) of phenylephrine. The occurrence of bradycardia and decreased cardiac output raise concerns among obstetric anesthesiologists. Nonetheless, these effects appear to have minimal impact on neonatal outcomes in healthy parturients and fetuses. In high-risk cases, such as maternal cardiac disease, placental insufficiency, and fetal distress, the impact of reduced cardiac output on neonatal and maternal outcomes is less evident but potentially more substantial.

Norepinephrine

NE is the primary catecholamine released by postganglionic adrenergic nerves and acts as a potent alpha-1 agonist with relatively modest beta-agonist activity. As a result, it increased the mean arterial pressure and stroke volume while increasing the HR, distinguishing it from phenylephrine. Unlike phenylephrine, NE can increase venous return due to its action on beta-adrenergic receptors in the veins. Moreover, it is the first-line vasopressor used in intensive care settings that increases arterial pressure and enhances organ perfusion [36]. Considering these properties, NE has garnered interest in obstetric anesthesia for its potential to maintain uteroplacental perfusion by managing spinal anesthesia-induced hypotension. Over the last decade, a growing body of literature has evaluated the safety and effects of NE on maternal and fetal outcomes during spinal anesthesia for cesarean sections.

Ngan Kee et al. [9] reported that NE effectively maintains BP while increasing HR and cardiac output compared to those in phenylephrine. Additionally, it yields similar maternal and fetal outcomes, including comparable umbilical ar-

Table 1. Summary of Available Vasopressors for Spinal Anesthesia-Induced Hypotension

	Ephedrine	Phenylephrine	Norepinephrine
Receptor	β_1, β_2, weak α	α_1	α_1, α_2, β_1
Mechanism of action	Indirect	Direct	Direct
Onset (min)	2–5	1 (immediate)	1 (immediate)
Duration of action (min)	60	5–10	5–10
Effect on heart rate	Increased	Reduced	Increased
Bolus doses	5–10 mg	50–100 μg	6 μg
Bolus doses*		0.25 μg/kg	0.05–0.1 μg/kg
Infusion rate	Not recommend	25–50 μg/min	
Infusion rate*		0.31–0.54 μg/kg/min	0.02–0.1 μg/kg/min

*Body weight adjusted doses.

terial and venous pH and blood gas values between the NE and phenylephrine groups [9]. These findings align with another study that assessed umbilical arterial pH and demonstrated that the effect of NE on neonatal outcomes was comparable to that of phenylephrine [37,38]. Despite its efficacy and safety, concerns exist regarding the potential occurrence of peripheral extravasation and tissue ischemia when high-dose NE is administered through the peripheral veins. However, no evidence in the literature supports this concern regarding the use of NE. In a recent study, peripherally infused NE in hypotensive patients for an average of 32 h showed no significant complications [39]. Previous studies suggest that diluted NE can be safely administered through the peripheral veins during obstetric anesthesia [10,40], although concerns remain regarding the use of such a potent agent in a noninvasive care setting [41,42].

ADMINISTRATION METHODS AND OPTIMAL DOSE

Vasopressor administration is typically categorized as an intermittent bolus or continuous infusion. Regardless of the method used, the administration of a vasopressor early or immediately after intrathecal injection is considered prophylactic. Several studies have reported the administration of a bolus after the onset of spinal anesthesia-induced hypotension as an intermittent, reactive, or rescue bolus.

Phenylephrine

Several studies have compared the efficacy of continuous infusions of prophylactic phenylephrine with that of reactive bolus administration. Results showed that continuous prophylactic infusion was superior to bolus administration alone, with a lower incidence of spinal anesthesia-induced hypotension, nausea, and vomiting. Although the total amount of vasopressors infused is significantly higher with continuous infusion [34], consensus guidelines recommend the use of continuous prophylactic phenylephrine infusion during cesarean sections under spinal anesthesia [1,43].

Allen et al. [44] reported that a prophylactic fixed-rate infusion of phenylephrine at 50 and 25 μg/min provided greater hemodynamic stability with fewer physician interventions and a lower incidence of reactive hypertension compared to those in doses of 75 and 100 μg/min.

However, considering the wide variations in body weight among individual parturients, it may be prudent to consider a weight-adjusted dose. Fixed-rate infusion without weight adjustment may result in under- or overdosing immediately after spinal anesthesia. In a study using a weight-adjusted dose of phenylephrine [45], the dose range was from 0.25 to 0.625 μg/kg/min. The study reported that the median effective dose (ED50) of 0.31 μg/kg/min (95% confidence interval [CI], 0.24– 0.36) and the 90% effective dose (ED90) of 0.54 μg/kg/min (95% CI, 0.46–0.76) were effective for preventing spinal anesthesia-induced hypotension. When the body weight range of 60–80 kg is applied to the ED90 value, the effective dose would be 32.4–43.2 μg/min, aligning with the findings of a previous study conducted by Allen et al. [44].

Although prophylactic infusion is initiated immediately after intrathecal injection, there may not be sufficient time to achieve the effective blood concentration of the vasopressor. Therefore, a combined prophylactic bolus strategy, followed by prophylactic infusion, can effectively prevent and treat hypotension that occurs immediately after the induction of spinal anesthesia. A typical rescue phenylephrine bolus dose of 50–100 μg is used [46]. Kuhn et al. [47] showed that an initial phenylephrine bolus of 0.25 μg/kg, followed by an infusion of 0.25 μg/kg/min, effectively maintained the systolic BP without causing adverse effects. In clinical practice, bolus administration is frequently used, either for its convenience or due to resource limitations. In such cases, employing a prophylactic bolus can significantly reduce the incidence of spinal anesthesia-induced hypotension [48].

Infusion rates can be manually adjusted by discontinuing or increasing the dose or rate to maintain BP at more than 80– 90% of its baseline value, based on the BP measured every 1–3 min. This adjusted rate reduces the BP variability by responding to reactive hypertension, bradycardia, and hypotension. Consequently, utilizing a variable weight-adjusted prophylactic infusion dose with adequate boluses (prophylactic and/or intermittent) helped maintain stable hemodynamics and reduced the total amount of vasopressors infused until delivery.

Norepinephrine

The relative vasoconstrictive potency ratio between NE and phenylephrine was approximately 10–13:1 [49]. Previous studies have established the ED90 of a bolus dose of NE to prevent hypotension during elective cesarean sections, ranging from 5.49–5.80 μg [40]. In a randomized controlled study (RCT) conducted by Sharkey et al. [50], an intermittent NE bolus of 6 μg was observed to provide a similar incidence

of hypotension but with a significantly lower incidence of bradycardia compared with an equipotent dose of 100 μg phenylephrine bolus (10.7% vs. 37.5%; P < 0.001). The use of a prophylactic bolus followed by a continuous infusion of NE proves to be more effective in treating spinal hypotension [51].

The administration of a higher bolus dose did not enhance the NE's effectiveness in preventing hypotension. A comparative study examined the efficacy and safety of two bolus doses of NE (6 and 10 μg). The rate of successful treatment of the first hypotensive episode was comparable between the two groups (88% vs. 85%). Although the HR was lower in the high-dose group, the administration of atropine was not required [52].

The continuous infusion of NE is more effective than bolus-only administration in reducing the incidence of hypotension. A double-blinded RCT compared NE boluses only (5 μg) against a prophylactic, manually adjusted continuous infusion rate (0– 5 μg/min) [53]. The continuous infusion group maintained a stable systolic BP closer to the baseline values and exhibited a lower incidence of spinal anesthesia-induced hypotension compared to that in the bolus-only group (17% vs. 66%, P < 0.001). Despite the significantly higher total amount of NE infused until the uterine incision, no adverse neonatal outcomes were reported.

One study investigated the optimal NE infusion dose, ranging from 0.025 to 0.1 μg/kg/min [51]. The infusion rates of 0.050 and 0.075 μg/kg/min effectively reduced the incidence of hypotension compared to that in an infusion rate of 0.025 μg/kg/min during cesarean sections. In another dose-finding study conducted by Wei et al. [54], the ED50 and ED95 values were 0.029 (95% CI, 0.008–0.042) and 0.105 (95% CI, 0.082–0.172) μg/kg/min, respectively. Subsequent dose-finding studies reported comparable ED50 and ED95 values of 0.029 (95% CI, 0.002–0.043) and 0.080 (95% CI, 0.065–0.116), respectively [55,56].

The variable infusion rate of NE, manually adjusted based on maternal BP rather than a fixed-rate, offers advantages. Hasanin et al. [38] compared the efficacy of various infusion rates of NE and phenylephrine. Both groups exhibited comparable incidence rates of hypotension, nausea, vomiting, and neonatal outcomes. However, the NE group required significantly fewer physician interventions than the phenylephrine group. A recent study by Belin et al. [57] analyzed the impact of manually controlled infusion on hemodynamic stability. Ephedrine was used for rescue management when hypotension persisted despite increasing the infusion dose. The NE group showed a significantly higher cardiac index compared with that in the phenylephrine group from the 5th min after spinal anesthesia to umbilical cord clamping. Although the phenylephrine group showed comparable BP and HR, this study highlights the advantages of NE in preserving cardiac index.

The primary consideration for anesthesiologists is to minimize BP variability and ensure stable hemodynamics during the cesarean section until the baby is delivered. Similar to phenylephrine, the manually controlled infusion rate, along with the bolus administration of NE, facilitates the effective management of hypotension with a minimal reduction in cardiac output and fewer complications associated with spinal anesthesia.

SPECIAL CIRCUMSTANCES

Pre-eclmapsia

The use of vasopressors in parturients with hypertension, including those with pre-eclampsia or eclampsia, requires caution during spinal anesthesia for cesarean sections. These patients tend to exhibit a lower incidence of hypotension following spinal anesthesia and require smaller amounts of vasopressors. A recent dose-response study [58] reported that the ED50 values of phenylephrine for preventing spinal anesthesia-induced hypotension were reduced by approximately 34% in parturient women with pre-eclampsia compared with those with normal BP (pre-eclamptic parturient: 47.6 μg [95% CI, 41.3–52.7]; normotensive parturient women: 72.1 μg [95% CI, 61.9–79.9]). Bolus doses required a reduced amount (50 μg for phenylephrine and 4 μg for NE), proving equally effective in treating hypotension in cesarean section [59].

A study by Higgins et al. [60] showed that a prophylactic phenylephrine infusion safely managed BP in women with preeclampsia. They controlled the infusion rate to maintain a systolic BP of ≥ 80% at baseline without exceeding 160 mmHg. Another study evaluated the effects of prophylactic NE (0.05 μg/kg/min) and phenylephrine infusion (0.625 μg/kg/min). Results showed no significant difference in the incidence of maternal hypotension or neonatal outcome in patients with pre-eclampsia undergoing cesarean sections [61]. However, bradycardia was significantly more common in the phenylephrine group, which is consistent with the findings of previous studies.

Therefore, titrating doses of phenylephrine and NE safely

manage BP and minimize hemodynamic variability in patients with pre-eclampsia. Recent guidelines advocate for tailoring the dose and type of vasopressor based on the individual BP ranges and HR in these patients [62].

Parturients receiving heart transplantation

With improvements in post-transplantation management, the number of obstetric patients receiving solid organ transplants has increased. Special consideration, particularly in heart-transplant recipients, is required when using vasopressors to manage spinal anesthesia-induced hypotension [63].

After heart transplantation, the sympathetic and parasympathetic nervous systems are denervated in the recipients, leading to altered physiological and pharmacological responses. Although the ability to respond to stress eventually develops, it differs from that of the normal heart [64]. Heart transplant recipients are preload-dependent, indicating that preload changes can significantly influence cardiac output. Following spinal sympathectomy, the cardiac output decreases secondary to reduced preload, and compensation through increased HR does not occur quickly. To increase the cardiac output, fluid infusion and changes to the left lateral position are necessary. The approach to using vasopressors in heart-transplant recipients differs; indirect vasopressors, such as ephedrine, are ineffective. Instead, direct vasopressors such as phenylephrine or NE should be prepared. Phenylephrine-induced bradycardia is generally uncommon. If HR control is needed, various direct agents are available, including isoproterenol to increase HR and propranolol, esmolol, and verapamil to slow HR. Since anticholinergic agents have different effects on denervated hearts, atropine does not increase HR. Neostigmine may produce a dose-dependent reduction in HR [63].

Pregnant women who have undergone heart-transplantation have a significantly higher incidence of pregnancy-related hypertensive disorders, including pre-eclampsia, compared with women who have not undergone heart-transplantation [65]. If pre-eclampsia occurs in patients undergoing cesarean sections, selecting the type of vasopressor and titrating the dose based on their physiological state is necessary. The optimal strategy for spinal anesthesia involves minimizing sudden changes in hemodynamics through careful control of local anesthetic doses, preparation of direct-acting vasopressors, fluid infusion, and changes in body position [66].

Persistent refractory hypotension and bradycardia

Increasing the dose of vasopressors and using anticholinergic agents may not effectively resolve hypotension and severe bradycardia (HR < 50 bpm). If these conditions persist, they can negatively affect uteroplacental perfusion pressure and neonatal outcomes. Anesthesiologists should promptly assess the hemodynamic status of the mother, considering undiagnosed hypovolemia, cardiac diseases, preeclampsia-induced heart failure, and a high sensory block [1]. A bolus of ephedrine or NE may be appropriate when phenylephrine infusion fails to correct spinal hypotension and exacerbates bradycardia owing to its exclusive alpha-receptor action. High spinal anesthesia can lead to an intensive lower limb motor block, leading to respiratory difficulty, profound hypotension, and ultimately cardiovascular collapse [67]. In such medical emergencies, aggressive resuscitation is necessary to stabilize hemodynamics. This may involve IV fluid infusion, additional inotropic and vasopressor infusions, respiratory support, and conversion to general anesthesia.

CONCLUSION

Spinal anesthesia-induced hypotension causes discomfort to the mother and poses potential risks to the neonate. Proactive measures for preventing and addressing hypotension typically include IV fluid co-loading, left uterine displacement, and vasopressor administration. The use of vasopressors is crucial in the management of spinal hypotension. Anesthesiologists should possess a comprehensive understanding of the different types of vasopressors, their characteristics, and appropriate clinical doses to ensure effective management of maternal hemodynamics.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author

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AUTHOR CONTRIBUTIONS

Writing - original draft: Hee-Sun Park. Writing - review & editing: Woo-Jong Choi. Conceptualization: Woo-Jong Choi.

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