Introduction

Spinal anaesthesia is the widespread prevailing neuraxial technique for caesarean delivery in many institutions because of the superior quality of surgical anaesthesia, rapid onset of action, excellent patient comfort, and fewer complication rates. However, its effect is not risk-free and is associated with significant hemodynamic changes. Yet, maternal hypotension is the common consequence of spinal anaesthesia resulting in adverse maternal and foetal events such as vomiting, nausea, decreased uteroplacental blood flow, and increased risk of foetal acidosis (1). Although the incidence of spinal-induced hypotension (SIH) varies according to definition of hypotension used, intravenous (IV) fluid loading and applied technique, it has been reported to be approximately 70–80% during elective caesarean delivery (2). Dahlgren et al. (3) and Teoh and Sia (4) described hypotension as a systolic blood pressure (SBP) less than 80 mmHg, whereas others used a decrease lower than 90% from baseline. Klöhr et al. (5) published a systematic literature search to classify the spectrum of definitions of hypotension reported in the literature. They searched 63 eligible publications (7120 patients) including 15 different definitions of hypotension. In this trial, they reported that SBP less than 100 mmHg and a decrease in SBP less than 80% baseline were the two most frequent definitions, noted in 20.6% and 25.4% of the publications, respectively.

Physiology of SIH

Although many reasons have been proposed to explain the mechanism of maternal hypotension, such as the height and density of the sensory block, the increased sensitivity to local anaesthetics (together with the effects of the sympathetic block during pregnancy), aortocaval compression of gravid uterus, and position of the parturient, the exact mechanism underlying maternal hypotension during spinal anaesthesia is complex and deserves to be examined (6). In literature, using a high dose of local anaesthetic in the spinal solution has been reported to be the most common cause of SIH (6).
Intrathecal administration of anaesthetics effectively remove sympathetic control of the vascular system. The induced sympathectomy causes vasodilation in both arteries and veins with a subsequent decline in systemic vascular resistance (SVR) (6-8). Traditionally, the main hypothesis underlying the mechanism of SIH was that a decline in central venous pressure (CVP) would reduce cardiac output (CO) and thus reduce arterial pressure. However, further studies assessing maternal hemodynamic variables have demonstrated that stroke volume (SV), CO, and heart rate (HR) increase in the first 15 minutes following the induction of spinal anaesthesia (7, 8). Langesaeter et al. (7) and Dyer et al. (8) used continuous minimally invasive blood pressure and CO monitoring to assess maternal hemodynamic outcomes in patients with spinal anaesthesia. The first author group noted a deep and rapid decrease in SVR with a compensatory increase in CO after spinal anaesthesia and reported that the most frequent response to spinal anaesthesia for elective caesarean section is a pronounced decline in SVR and partial compensation from increased HR and SV (7). The latter group demonstrated similar changes in parturients, i.e., there was a 25% increase in CO and an initial 36% decrease in SVR after the induction of spinal anaesthesia (8). Accordingly, a significant decrease in SVR ensues, implying that the loss of arteriolar tone is the major mechanism leading to hypotension. Therefore, vasopressors have currently become the mainstay for the management of SIH.

Vasopressors in SIH

For decades, ephedrine was considered to be the best vasopressor for use with maternal hypotension because of its better protection of uteroplacental blood flow in experimental studies compared with alpha-adrenergic agonists such as phenylephrine, metaraminol, or norepinephrine (9). At that time, alpha-adrenergic agonists had been accused of causing vasoconstriction on the uterine vascular bed, which led to foetal acidosis. Greiss reported that although SIH was corrected in pregnant sheep, phenylephrine and norepinephrine caused significant uterine vessel vasoconstriction to reverse the impact of increased blood pressure on uterine blood flow (9). However, animal experiments do not often translate into replications in human trials, and further and larger series of clinical trials have demonstrated that phenylephrine, norepinephrine, and other alpha-agonists are not only more effective than ephedrine at preventing hypotension but also associated with a lower risk of foetal acidosis compared with ephedrine.

Traditionally, alpha-adrenergic agonists became the agents of choice for the management of SIH and can be identified as cardiotonic agents. Pharmacologically, cardiotonic agents can be classified as sympathomimetic amines and non-adrenergic inotropes (Table 1). Sympathomimetic amines can also be separated into catecholamines (both synthetic exogenous and natural endogenous) and non-catechol sympathomimetics (10).

Specific Vasoactive Receptor Effects

Each sympathomimetic amine has its own unique receptor affinities and, therefore, its own unique cardiovascular stimulatory profile. α1 agonists lead to vasoconstriction of arteries and veins and result in reflex bradycardia. α2 agonists act as a feedback mediator to decrease the release of norepinephrine from nerve terminals and lead to minor vasoconstriction. β1 agonists have direct inotropic and chronotropic effects in atria and ventricles. β2 agonists contribute to about 20% of endogenous contractility and primarily have direct vasodilation of kidneys, skin, skeletal muscles, pulmonary, and visceral arteries and produce bronchodilation. DA1 (dopaminergic) agents have an effect on splanchnic and renal vasculature (splanchnic vasodilation). DA2 agents decrease norepinephrine release at presynaptic receptors and thereby cause vasodilation (feedback inhibition) (10). Commonly used vasopressors and their affinity for primary receptors are shown in Table 2.

Methoxamine

Methoxamine is a dense vasoconstrictor agent with a selectivity for α1 receptors. It is used by both intravenous and intramuscular routes to increase blood pressure by raising SVR during anaesthesia but leads to reflex bradycardia. At present,
its clinical usage is abandoned due to its detrimental effect on uterine blood flow and negative effect on foetal acid-base status (11). In literature, there are limited studies on the efficacy of methoxamine for the management of SIH. Further and larger series of studies are needed to consider the routine use of methoxamine for the management of SIH.

**Metaraminol**
Metaraminol (metadrine) has both mixed α and β receptor agonistic effect, but at clinical doses, its α effect is superior to that of β. It causes active vasoconstriction due to its very strong α agonistic effect. Metaraminol shifts with norepinephrine at the end of sympathetic nerve and causes tachyphylaxis.

Although some studies have shown that metaraminol was more effective than phenylephrine and ephedrine, others have failed to demonstrate any advantage in the preservation of both maternal blood pressure and foetal pH during SIH (12, 13). McDonnell et al. (12) compared metaraminol and phenylephrine infusions for the prevention of SIH and found that metaraminol was superior to phenylephrine with respect to foetal outcomes. However, more recently, Chao et al. (13) presented a meta-analysis by investigating four randomised controlled trials and compared metaraminol with other vasopressors during spinal anaesthesia. They reported that prophylactically administrated metaraminol seems to be more effective than ephedrine, and at least similar to phenylephrine during SIH. Metaraminol was also related with a higher incidence of reactive hypertension, a lower incidence of foetal acidosis, a higher umbilical arterial pH, and a lower incidence of maternal outcome than ephedrine. Given the information in the literature, further studies are needed to support the daily use of metaraminol in obstetric anaesthesia.

**Mephentermine**
Mephentermine has both α and β receptor agonistic effects and causes the release of both norepinephrine and epinephrine. It increases CO and SBP. HR variables depend on the vagal tonus. Administered intravenously (bolus dose 3–5 mg, infusion dose 2–5 mg min⁻¹), the maximum onset of action begins within 5 min and lasts for 15–30 min. When used intramuscularly (25–50 mg), its duration of action varies between 1 and 4 h. Compared with ephedrine, mephentermine has been shown to have a similar efficacy on the incidence of maternal hypotension and neonatal outcomes (14). Mohta et al. (15) compared mephentermine sulfate and phenylephrine hydrochloride infusions for the prevention of SIH and found that both drugs have a similar effect on the prevention of SIH and neonatal outcomes.

**Ephedrine**
Ephedrine has both α and β receptor agonistic activities and leads to the release of norepinephrine from sympathetic neurons by indirect action. β₁ effect increases the heart rate and cardiac contractility, whereas α effect causes peripheral vasoconstriction. It has a nearly slow onset and long duration of action. The consumption of the presynaptic norepinephrine storage after sequential injections causes tachyphylaxis (9, 10).

Ephedrine has widely been used for the prophylaxis and treatment of maternal hypotension for years. Gunasekaran et al. (16) compared rapid and slow bolus of ephedrine adminis-
istration in patients undergoing caesarean section with spinal anaesthesia and found that the slow bolus dose was more effective, but with less foetal acidosis in treatment of SIH than rapid bolus dose of ephedrine. Alday Muñoz et al. (17) compared the effect of phenylephrine and ephedrine infusions for the prevention of SIH during caesarean section and noted that both drugs have a similar prophylactic effect on the incidence of maternal hypotension, but there was a higher incidence of hypertension and bradycardia with phenylephrine.

A recent meta-analysis from Veeser et al. (18) showed that ephedrine was associated with a 5-fold increased risk of foetal acidosis than phenylephrine, probably because ephedrine crosses the placenta and increases the concentration of catecholamines in the foetal circulation. Therefore, anaesthetists have begun to search for new vasopressors for the prevention and treatment of SIH. However, Heesen et al. (19) failed to demonstrate any difference in incidence of foetal acidosis (umbilical arterial pH <7.2) between phenylephrine and ephedrine for high-risk caesarean sections in their meta-analysis. However, despite the growing evidence regarding the potential side effects, ephedrine was still routinely used by more than 70% of clinical anaesthetists for the prevention and treatment of SIH.

**Phenylephrine**

A pure α-adrenergic agonist agent, phenylephrine has both indirect and direct sympathomimetic properties; the indirect effect of phenylephrine results from the release of norepinephrine from nerve terminals’ storage sites. Unlike ephedrine, it lacks β-mimetic activity, but increases SVR and mean arterial pressure (MAP) via arteriolar vasoconstriction with its α-mimetic effect. A reflex decline in HR is typical due to the lack of direct inotropic and chronotropic activity which results in low CO (2, 10).

A decrease in CO with phenylephrine led to concerns as some authors have advocated that placental perfusion and oxygen delivery to foetus are mainly related with maternal CO and HR rather than SBP (20). However, further and more recent studies demonstrated that a greater CO is not always related with better maternal or neonatal outcomes in high-risk parturients (20, 21). In that study, the authors also stated that increasing CO levels might especially be important in high-risk parturients such as compromised foetal status, placental insufficiency, or maternal cardiac disease (21).

Mohta et al. (22) compared phenylephrine (100 µg) and norepinephrine (5 µg) boluses for treatment of SIH and noted a non-significant difference in maternal bradycardia between the two groups but with lower umbilical artery pH values with norepinephrine. Xu et al. (23) showed that intramuscular use of phenylephrine (5 mg) for the prevention of SIH provided a more stable maternal hemodynamics and better neonatal acid-base status than prophylactic use of IV 100 µg phenylephrine and placebo. Lee et al. (24) studied the effects of prophylactic bolus injection of phenylephrine on SIH and found that 1.5 µg kg⁻¹ of phenylephrine was a suitable dose for reducing the incidence of SIH.

A previous study by Ngan Kee et al. (20) reported the potency ratio of norepinephrine: phenylephrine as 20:1; however, this ratio more recently was reconsidered by the first author. He conducted a dose-response study of norepinephrine and phenylephrine for rescuing the first episode of maternal hypotension during caesarean delivery and calculated an ED₉₀ of 18 µg versus 239 µg for norepinephrine and phenylephrine, respectively during caesarean delivery, a potency ratio of approximately 13:1 (25). This result suggests that compared with a dose of phenylephrine 100 µg, the equivalent dose of norepinephrine is 8 µg (95% CI, 6 to 10 µg).

Studies have demonstrated that decreases in mean arterial pressure led to significant declines in maternal regional cerebral blood volume and oxygenation during SIH (26, 27). Hirose et al. (26) showed that prophylactic phenylephrine infusion (at 25 µg min⁻¹) is effective in the protection of regional cerebral blood volume and oxygenation during SIH. However they observed that a phenylephrine infusion at 50 µg min⁻¹ significantly decreased the tissue oxygenation index, although total haemoglobin and mean arterial pressure was maintained. Finally, Xu et al. (27) published a meta-analysis and systematic review comparing safety and efficacy of phenylephrine and norepinephrine for the management of SIH. They found similar results with respect to the prophylaxis and treatment of hypotension (OR 0.64, 95% CI, 0.37-1.10, p=0.11).

**Norepinephrine**

Norepinephrine is a biosynthetic precursor of epinephrine and is commonly used for the management of shock and hypotensive crisis. It has both α and β effects. The weak β-agonist-mediated positive chronotropic effect balances its negative chronotropic action due to its potent α-effect. It has a lower tendency than phenylephrine to cause bradycardia (10, 20).

Both bolus and infusion doses can be used for the management of SIH in a prophylactic or reactive manner. However, a recent consensus statement reports that vasopressors should be administered preferably prophylactically and routinely as hypotension is frequent in caesarean section patients during spinal anaesthesia (28). Onwochei et al. (29) performed a dose-finding study for the prevention to SIH with intermittent boluses norepinephrine and found that intermittent 6 µg of IV norepinephrine boluses to prevent SIH are feasible. Ngan...
Kee et al. (20) compared the effects of norepinephrine 5 µg mL⁻¹ and phenylephrine 100 µg mL⁻¹ infusions for the management of SIH. They found a greater HR and higher CO with norepinephrine and similar umbilical artery pH when compared with phenylephrine. However, Mohta et al. (22) did not find any difference in umbilical artery pH between norepinephrine (5 µg) and phenylephrine (100 µg) boluses.

Hasanin et al. (30) assessed the effect of prophylactically administered norepinephrine (0.05 µg kg⁻¹ min⁻¹) and phenylephrine (0.75 µg kg⁻¹ min⁻¹) infusion on the incidence of post-spinal hypotension. They observed a similar incidence of post-spinal hypotension between groups, but a lower incidence of bradycardia and reactive hypertension with the norepinephrine group. Sharkey et al. (31) compared intermittent boluses of norepinephrine (6 µg) and phenylephrine (100 µg) for the treatment to SIH and noted a less fluctuation in HR and CO and a significant reduction in the incidence of bradycardia with norepinephrine. Finally, Xu et al. (27) in a systematic review and meta-analysis confirmed a lower incidence of bradycardia with norepinephrine than with phenylephrine.

**Epinephrine**

Epinephrine, the most potent inotrope of the sympathomimetic drugs, is produced by the adrenal gland during stressful events. It has high affinity for α₁-, β₁-, and β₂-adrenergic receptors in a dose-dependent fashion. β effects predominate at low doses and increase cardiac contractility, CO, and HR, while α₁ effects are more significant at higher doses and lead to increase in afterload and MAP (10).

In obstetric settings, epinephrine is a less familiar drug to anaesthesia providers for preventing and treating spinal hypotension during caesarean delivery. In the literature, there is only one historical study comparing the effect of epinephrine with phenylephrine in the treatment of hypotension after hyperbaric tetracaine spinal anaesthesia (32). However, in North America, epinephrine, phenylephrine, and ephedrine have been recommended as first-choice vasoressors (33). Further, Kinsella et al. (28) recommended that epinephrine should only be used for patients with circulatory collapse.

Norepinephrine is a biosynthetic precursor of epinephrine and at present is commonly used for the management of SIH. The question remains, why is epinephrine, with delicate dose titration, ruled out for routine prophylaxis and treatment of SIH? Possibly, in the near future, new research will be available for the management of SIH with epinephrine.

**Dopamine**

Dopamine has a rapid onset and a brief duration of action (5–10 min) and stimulates dopaminergic (DA1 and DA2) as well as β- and α-adrenergic receptors in a dose-dependent fashion (34). In fact, in very low doses, dopamine has only dopaminergic action and causes vasodilation and improved perfusion in renal, mesenteric, and splanchnic beds. β-adrenergic receptor stimulation results in augmented inotropic activity and increased HR and CO. The dose of dopamine causing vasoconstriction and increasing blood pressure (α effect) in both healthy volunteers and parturients is extremely variable, but usually exceeds 6 to 10 µg kg⁻¹ min⁻¹. Limited data are present on the clinical use of dopamine for the management of SIH. Clark et al. (33) investigated the effect of dopamine in parturients undergoing caesarean delivery with spinal anaesthesia and found preserved maternal blood pressure during caesarean section, but with lower umbilical artery and vein pO₂ levels compared to control. Therefore, its use in clinical obstetrics fell out of favour nearly four decades ago.

**Theodrenaline**

Theodrenaline is a combination of norepinephrine and theophylline. In Germany, theodrenaline is commonly used with cafédrine. Cafédrine is a combination of norephedrine and theophylline. A combination of cafédrine and theodrenaline, called Akrinor, is used for the treatment of SIH during caesarean section. Cafédrine/theodrenaline, in a ratio of 20:1, has been used for the treatment of hypotension in emergency medicine and anaesthesia since 1963 (36). Studies show that 86.2% of hospitals in Germany use cafédrine/theodrenaline for the treatment of SIH during a caesarean section (36).

The proposed mechanism of action of cafédrine/theodrenaline in cardiomycocytes is increased inotropic activity. However, the norephedrine component releases noradrenaline from nerve endings and activates the β₁-adrenoeceptor stimulation. In the meantime, released endogenous norepinephrine may also act as a partial agonist at the α₁-adrenoeceptor, thereby mediating vasoconstriction by itself. The norepinephrine component of theodrenaline activates the α₁-adrenoceptor of the vascular smooth muscle cell and leads to vasoconstriction (36).

Cafédrine/theodrenaline leads to a rapid increase in systemic blood pressure that is characterised by increased preload, SV, and CO. SVR and HR remain mostly unchanged. One of the advantages of cafédrine/theodrenaline combination is that it can be administered as a bolus without dilution (36). The onset of action is faster, which may be beneficial in the treatment of hypotension. Clemens et al. (37) investigated the efficiency of cafédrine/theodrenaline combination on the incidence of SIH retrospectively and reported a preserved maternal blood pressure without detrimental effect on umbilical cord pH and APGAR scores.

**Ondansetron**

Sympatholysis during spinal anaesthesia induces a decrease in SVR and causes vasodilation in both arteries and veins. A decrease in venous return to the right heart, produced by
sympatholysis, activates Bezold-Jarisch reflex (BJR) and leads to vasodilation, bradycardia, and hypotension (38).

Ondansetron has been reported to inhibit the BJR by blocking serotonin binding to 5-HT3 receptors in the left ventricle and leads to elevated blood pressure and heart rate (39). In many studies, ondansetron has been noted to reduce the incidence of SIH and vasopressor consumption in parturients undergoing caesarean delivery with spinal anaesthesia (40). Recently, our study group assessed the effect of prophylactic ondansetron on the incidence of SIH and noradrenaline consumption. We noted that IV ondansetron (8 mg) given 5 min before spinal anaesthesia attenuated but did not prevent SIH in parturients undergoing elective caesarean delivery (41).

Vasopressin
Vasopressin is primarily secreted from posterior hypotalamus and released into the bloodstream to restore arterial hypertension and hypovolemia and to lower high serum osmolality (42). It causes vasoconstriction by stimulating V1 and V2 receptors that are mainly found on vascular smooth muscles and lead to pulmonary vasodilatation, possibly because of the stimulation of endothelial nitric oxide release (42). In the literature, two studies used IV infusion of vasopressin with success to prevent maternal hypotension resulting from sympathetic blockade in a parturient with primary pulmonary hypertension. However, vasopressin should be reserved for circulatory collapse or patients who do not respond to volume infusion and catecholamine administration (43).

Pre-eclamptic Patients and Vasopressors
Previous studies showed that pre-eclamptic patients were less likely to develop hypotension after spinal anaesthesia than healthy pregnant or non-pregnant women (44). In pre-eclampsia, an imbalance between pro- and anti-angiogenic growth factors leads to vascular epithelium damage and failure of the sympathetic vascular system, which results in consistent vasoconstriction. In contrast, a healthy pregnant woman is very sensitive to spinal anaesthesia because of a controlled balance of the vascular tone (45). Responses to endogenous pressors such as angiotensin II are diminished because of alteration in the endothelium-dependent factor of vascular smooth muscles. Additionally, there is an increased synthesis of vasodilator prostaglandins and nitric oxide leading to increased dependence on sympathetic vascular tone in a healthy pregnancy (44). In a retrospective study, comparing the neonatal acid-base status of phenylephrine and ephedrine for the treatment of SIH in pre-eclamptic patients undergoing caesarean section, the authors did not find any difference in umbilical artery pH values between the two groups (46).

Sivevski et al. (47) investigated the incidence and severity of SIH in pre-eclamptics and healthy parturients and found that the incidence and severity of spinal-induced hypotension in pre-eclamptic patients were less than in healthy women. They also stated that healthy parturients required higher doses of vasopressors, both ephedrine (16.5±8 vs. 6.0±2.0 mg) and phenylephrine (105±25 mg), than pre-eclamptic parturients. Recently, Dyer et al. (48) evaluated the effect of hemodynamic changes of colloid preload and phenylephrine and ephedrine administered for SIH during caesarean section in parturients with severe early-onset pre-eclampsia. They reported that CO increased in response to spinal anaesthesia in parturients with pre-eclampsia and that a small dose of phenylephrine (50 µg) restored the hemodynamic changes more effectively than ephedrine.

Higgins et al. (49) conducted a study comparing the effect of prophylactic ephedrine and phenylephrine infusions on umbilical blood gas, particularly pH analysis in parturients with pre-eclampsia during spinal anaesthesia. They were unable to demonstrate a beneficial effect of phenylephrine on umbilical artery pH compared with ephedrine. Furthermore, their findings suggest that phenylephrine may not have a clinically important advantage compared with ephedrine with regard to improved neonatal acid-base status when used to prevent SIH in parturients with pre-eclampsia.

Conclusion
This review shows that vasopressors should be administered preferably routinely and prophylactically as the incidence of maternal hypotension is frequent in parturients undergoing caesarean delivery with spinal anaesthesia. At present, phenylephrine (25 µg min⁻¹) is probably the most popular vasopressor of choice for the prevention and treatment of SIH. However, noradrenaline may be a promising substitute for phenylephrine because of its better CO and HR profile.

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