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Review article

Post-spinal anesthesia hypotension during cesarean delivery, a review article

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ABSTRACT

Maternal hypotension is a common complication after spinal anesthesia for cesarean delivery. Prevention and treatment of post-spinal hypotension (PSH) in cesarean delivery has been frequently investigated.

Fluid loading is superior to no-fluid regimen; however, the incidence of PSH is still high with all fluid loading protocols; thus, the use of fluid loading as a sole method for prophylaxis might be not satisfactory for many anesthetists. Phenylephrine is the preferred vasopressor for prevention and management of PSH in most cases. Ephedrine may be more beneficial in patients with bradycardia, patients with uteroplacental insufficiency and pre-eclamptic patients. Norepinephrine infusion was recently investigated as an alternative for prophylaxis of PSH with minimal cardiac side effects.

The high incidence of PSH with most of the pharmacological and non-pharmacological methods suggests the need for multimodal protocols for prevention and management of this problem. PSH in cesarean delivery is a common daily situation facing all anesthetists; thus, future research should focus on simple and rapid protocols that can be easily applied by anesthetists with moderate and low experience with minimal need to complex devices or costly drugs.

Contents

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1. Introduction

Spinal anesthesia is the popular route of anesthesia in parturients for cesarean delivery [1]. Maternal hypotension is a common complication after spinal anesthesia resulting in adverse maternal and fetal outcomes [2,3]. Prevention and management of post-spinal hypotension (PSH) is continuously investigated [4,5]. In this article, we are giving an updated review for prevention and management of PSH in cesarean delivery. Gaps in literature, areas of unclear evidence, as well as future thoughts are also highlighted.

The basic components of management of PSH are: (1) Fluid loading. (2) Pharmacological agents. (3) Positioning protocols.

2. Fluid loading

Although the use of fluid loading regimens has been considered as a classic practice in obstetric anesthesia, recent evidence has questioned its value [3]. Some authors reported that spinal anesthesia in obstetric population is accompanied by an increase rather that decrease in cardiac output [6–8]. This finding makes fluid loading for prevention of PSH an unlikely hypothesis. Moreover, fluid loading in parturients has been reported to disrupt glycocalyx [9]. Glycocalyx is a carbohydrate-rich layer lining the endothelium that plays a role in maintaining endothelial integrity. Destruction of endothelial glycocalyx was reported as a cause for failure of fluid loading in prevention of PSH [9].

2.1. Preloading

Although crystalloid preloading is superior to the "no fluid regimen", the incidence of PSH with all preloading regimens is still high [4,5]. According to the latest Cochrane database reviews, the colloid preloading regimen may be better than crystalloid preloading [5]; however, later Randomized Controlled Studies comparing colloid and crystalloid preloading showed conflicting evidence [8,10–13].

2.2. Co-loading

The most accepted explanation for the limited value of fluid preloading is the rapid distribution of administrated fluids in the extravascular space [14]. This was the cause of the evolution of the concept of fluid co-loading where rapid fluid administration is started simultaneously with spinal block. With co-loading, fluid re-distribution might be minimized because of simultaneous vasodilatation [15].

Most studies reported that co-loading is superior to (or at least the same as) preloading when comparing the two protocols using the same type of fluid. Crystalloid co-loading is superior to crystalloid preloading [16–19] and similar to colloid preloading [20]. Colloid co-loading is not superior to colloid preloading [21–24].

With comparing fluids of different types, crystalloid co-loading was similar to colloid co-loading [25]. The fluid volume needed with colloids is less than the volume needed with crystalloids.

2.3. Goal directed fluid therapy

Many protocols of goal directed fluid therapy (GDFT) have been introduced aiming to optimize perioperative hemodynamic state and improve patient outcome. According to a recent RCT, GDFT aiming for optimization of stroke volume was associated with lower incidence of PSH compared to control group [26].

2.4. Important notes

The incidence of PSH is obviously high with all fluid loading regimens.

1. Important limitations in fluid loading studies included: the high variability in the volume regimens and other cofactors such as combination of fluids and vasopressor.
2. The only meta-analysis comparing co-loading with preloading (showing no difference between both regimens) included RCTs for both colloids and crystalloids regimens without subgroup analysis [27].
3. Most of "preload versus co-load" and "crystalloid versus colloid" studies didn't include control group that didn't receive any fluid loading regimen [16,17].

2.5. Collective evidence

With the available evidence, we could assume that fluid co-loading is preferred to preloading because it carries more success (or at least the same results) in prevention of PSH with the advantage of being less time consuming. We also suggest the use of crystalloids over colloids because of the lower cost with unclear benefit for colloids. We suggest that using fluid loading protocols is not sufficient to achieve satisfactory clinical results (Table 1).

3. Vasopressors

3.1. Choice of the vasopressor

The use of vasopressors is more widely accepted as an effective method for decreasing PSH than fluid loading [3]. Phenylephrine (PE) is preferred vasopressor in prevention and treatment of PSH because of: faster onset [7], less incidence of fetal acidosis [28], less placental passage [29], less maternal nausea and vomiting despite the similar incidence of PSH [30,31]. Norepinephrine was recently investigated as an alternative to PE with less cardiac depression with promising results [32,33]; however, more research is warranted for reaching the optimum dose. In addition to its potent antiemetic properties, ondansetron was reported as a prophylactic drug from PSH with minimal side effects [34]. Although it is less recommended, ephedrine still has a role in some situations:

Table 1
Fluid loading protocols.

Protocol	Main results	Type of study
Crystalloid preload versus no fluid regimen.	Crystalloid preload is superior [4,5]	meta-analysis
Crystalloid preload versus colloid preload	Colloid preload is superior [5]	meta-analysis
Crystalloid preload versus crystalloid co-load	Co-load is superior [16–18]	RCT
Crystalloid co-load versus colloid co-load	No difference [25]	RCT
Crystalloid co-load versus colloid preload	No difference [20]	RCT
Colloid preload versus colloid co-load	No difference [21–24]	RCT

RCT: randomized controlled trial.

(A) Bradycardia (baseline bradycardia or PSH associated with bradycardia): The negative effect of PE on maternal cardiac output makes ephedrine the drug of choice in cases associated with bradycardia [35].
(B) Patients with compromised cardiac function: although no studies compared both drugs in this population, the negative effect of PE on cardiac output is still considered a limitation for its use in these patients [3].
(C) Uteroplacental insufficiency: PE decreases maternal cardiac output (CO) and increases peripheral vascular resistance, and consequently decreases uteroplacental perfusion [31]. Only one RCT was conducted on patients with potential fetal compromise reporting no difference between ephedrine and PE with regard to fetal Apgar scores and umbilical pH [36]. Another RCT was conducted on patients with acute fetal compromise showing no difference between ephedrine and PE in fetal umbilical pH [37]. However, no study reported the direct effect of both drugs in uteroplacental blood flow.
(D) Pre-eclampsia
- Administration of alpha agonists might decrease uteroplacental perfusion in these patients with higher baseline systemic vascular resistance [35].
- Unlike other parturients, pre-eclamptic patients don't have increased cardiac output after spinal anesthesia [38].
- Only one retrospective study reported no significant differences between ephedrine and PE on fetal outcome in pre-eclamptic patients [39]. However, the evidence for the best drug in those patients is still low.

3.2. Dose of the vasopressor

Many PE dosing protocols were investigated. The most popular dosing regimens are: 1- bolus regimens. 2- Fixed infusion regimens. 3- Variable infusion regimens.

- *PE boluses versus infusion:* Das Neves et al. [40] reported that prophylactic PE infusion is superior to prophylactic PE bolus and therapeutic PE bolus. On the other side, Doherty et al. reported more stable hemodynamics with bolus regimen; however, this finding had no impact on maternal and fetal outcomes [41].
- *PE bolus dose:* George at al. [42] reported 150 μg as an optimum therapeutic PE dose for management of PSH. With regard to prophylaxis, Tanaka et al. [43] reported 122 μg as the 95% effective dose. A recent RCT [44] showed 1.5 μg/kg to be superior to 1 μg/kg and 2 μg /kg as a prophylactic bolus for prevention of PSH.
- *Phenylephrine infusion dose:* Doses ranging from 10 μg/min to 100 μg/min have been investigated. The most recent dose finding studies [45,46] recommended a dose of 25–50 μg/min. A higher incidence of PSH was reported with the lower dose (25 μg/min) [45,46]. A higher incidence of reactive hypertension [45] and bradycardia [46] were reported with the higher dose (50 μg/min).
- *Variable manual and automated infusion systems:* In the last few years, different variable manual and automated PE infusion systems have been developed. Variable manual infusion rate was superior to intermittent bolus regimen [47]. Closed-loop automated feedback infusion was superior to manual controlled infusion [48]. A double vasopressor automated system (PE if SBP <90 mmHg and ephedrine if SBP <90 mmHg with heart rate <60 bpm) was superior to manual bolus vasopressor protocol [49].

3.3. Important note

- Studies that investigated different vasopressor protocols varied regarding: fluid loading therapy – local anesthetic dose – duration of vasopressor infusion.
- Maternal and neonatal final outcomes were nearly the same with all protocols.

3.4. Collective evidence

We suggest that using PE is the preferred vasopressor in management of PSH especially in mothers with heart rate more than 60 bpm and with good cardiac reserve. The optimum dose still need more research; however, a single bolus of 1.5–2 μg/kg seems to be simple and effective with no need to sophisticated devices. Norepinephrine seems to be a new attractive alternative to PE with less cardiac depression; however, the proper dose of norepinephrine needs more research (Table 2).

4. Positioning protocols

Most of positioning protocols have one of the two following targets: (1) Relieving aortocaval compression. (2) Increasing venous return.

According to the latest Cochrane reviews [5,50], the evidence is not adequate to recommend operating table tilting or flexing, the use of wedges or mechanical displacers, leg wrapping or sequential compression devices, head down and head up poisoning. Left tilting is superior to right tilting; however, it is less effective than manual displacers [50].

The value of left lateral tilting in improvement of maternal cardiac output is unclear. Three recent studies investigated the effect of tilting on maternal hemodynamics. The first study by Lee et al. [51] reported an increased CO with 15° left tilting. In the second study, Kundra et al. reported that moving a full-term parturient from left lateral position to left-tilted position prevented aortocaval compression better than moving the parturient from supine position to left tilted position [52]. Finally, Higuchi et al. [53] did not report any improvement of CO except with 45° left tilting. It is to be noted that the three aforementioned studies were performed in non-anesthetized full-term pregnant women. More

Table 2
Vasopressor protocols.

Protocol	Main results	Type of study
Ephedrine versus PE	Both have the same effect on hypotension. PE is associated with less fetal side effects [28]	meta-analysis
PE bolus versus PE infusion	Controversial [40,41]	RCT
PE bolus doses	Therapeutic dose (150 μg) [42], Prophylactic doses (122 μg) [43] and (1.5μ/kg) [44]	RCT
PE fixed infusion doses	The best dose ranges between 25 and 50 μg/min [45,46]	RCT
Variable manual PE infusion versus boluses	Variable manual infusion is superior [47]	RCT
Automated PE versus manual infusion doses	Automated infusion is superior [48]	RCT
Automated PE versus norepinephrine infusion	Both drugs were equally effective [32]	RCT
Ondansetron versus placebo	Ondansetron is superior [34]	meta-analysis
Norepinephrine versus PE	Both drugs are comparable [32,33]	RCT

PE: Phenylephrine, RCT: Randomized controlled trial.

research is warranted for detection of the effect if patient tilting after anesthesia. Lateral positioning during spinal block showed better hemodynamics compared to sitting position [54]. More studies are needed to investigate the hemodynamic effects of patient tilting after spinal block.

5. Gaps in literature and conclusions

Fluid loading for prophylaxis from PSH is superior to no-fluid regimen. The use of co-loading protocols seems to be less time consuming with better (or at least similar) effect than preloading. It is to be noted that the incidence of PSH is still high with all fluid loading protocols; thus, the use of fluid loading as a sole method for prophylaxis might be not satisfactory for many anesthetists.

Although phenylephrine produces less fetal acidosis than ephedrine, there is no evidence supporting phenylephrine on more global neonatal outcomes. The theoretical risk of phenylephrine use in pre-eclamptic patients and patients with uteroplacental insufficiency should be an area of future investigation. Norepinephrine was recently reported as an alternative to phenylephrine with less cardiac depression; however, the optimum norepinephrine dosing regimen needs more research.

Many vasopressor dosing protocols were reported for prevention and management of PSH. Evidence supporting either infusion or bolus PE regimens is not clear. Automated PE infusion systems seem to be better than manual infusion systems. Final maternal and neonatal outcomes are the same with most protocols.

The primary outcome for most studies investigating different pharmacological and non-pharmacological methods was usually the incidence of PSH; thus, the ability for these studies to investigate neonatal outcome is low. Studies designed and powered to detect the impact of different measures on neonatal outcome are warranted.

No single measure reduced the incidence of PSH in cesarean delivery to a clinical satisfactory level. Future research should focus on multimodal combinations of pharmacological and non-pharmacological methods for prophylaxis from PSH.

Finally, as CS is a very common operation performed nearly in every hospital, we assume that dealing with PSH is a daily situation facing anesthetists with variable levels of experience; thus, future research should focus on simple and rapid protocols that can be easily applied by anesthetists with moderate and low experience with minimal need of complex devices or costly drugs.

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