Review Article
ISSN (Print): 2394-6954
ISSN (Online) : 2394-9775
Karnataka Anaesthesia Journal *Vol 17(1&2), January-June 2019, p. 5-11* *DOI: 10.4103/kaj/2019/v17i1-2/144625*

Vasopressors in Obstetric Anaesthesia: Current Considerations

Safiya I. Sheikh* and K. S. Sushma

Department of Anaesthesiology, Karnataka Institute of Medical Sciences, Hubli – 580022, Karnataka, India; ssafiya11@yahoo.com

Abstract

Caesarean section is a routine operation in each and every hospital and spinal anaesthesia for it, is now the popular technique. Unfortunately maternal hypotension is the most common unwanted consequence of spinal anaesthesia that causes maternal and foetal adverse effects. Vasopressors are the most reliable method for management of hypotension. Ephedrine and phenylephrine are commonly used drugs to treat hypotension. Lot of research and clinical data are supporting the use of phenylephrine over ephedrine. New research is also emanating showing norepinephrine as an effective alternative to phenylephrine. Automated computer control system using multidrug vasopressor infusion may play a potential role in future.

Keywords: Ephedrine, Maternal hypotension, Norepinephrine, Phenylephrine, Vasopressors

1. Introduction

Caesarean section with central neuraxial blockade allows a woman to experience the birth of her child.

Spinal anaesthesia has long been established as the anaesthetic technique of choice for caesarean section, because, it is an easily achievable, fast and reliable technique[1,2]. However it is often associated with maternal hypotension with significant maternal consequences such as reduced perfusion of vital organs, nausea, vomiting, dyspnoea and also adverse effect on foetus which includes depressed APGAR score and umbilical artery acidosis[3]. Prevention and treatment of post-spinal hypotension during caesarean section has been frequently investigated.

After adequate fluid rescuscitation, vasopressors are used to counteract hypotension after neuraxial anaesthesia in obstetrics as they lead to increase in systemic vascular resistance and rise in mean arterial pressure.

Routinely used vasopressors are:

1. Directly acting selective alpha adrenergic receptor agonist eg: phenylephrine and methoxamine.
2. Directly and indirectly acting eg: mephenteramine, metaraminol and ephedrine.

In this article we review available facts about pathophysiology of hypotension, non pharmacological, pharmacological management and recent trends for various vasopressors used in obstetric anaesthesia[4].

2. Literature Search

We performed a systematic literature search in the data base websites of PubMed, Google scholar, Sci-hub with key words, "vasopressors, maternal hypotension, ephedrine, phenylephrine, norepinephrine". We also referred to international consensus guidelines, American Society of Anaesthesiology (ASA) guidelines, National

**Author for correspondence*

Institute of health and Care Excellence (NICE) guidelines for management of post spinal hypotension during caesarean section.

3. Maternal Hypotension

Hypotension is a very common consequence of sympathetic vasomotor block caused by spinal anaesthesia for caesarean section[5]. It is defined in absolute terms as Systolic Blood Pressure (SBP) of 90 or 100 mmHg or in relative terms as a percentage that is 20% fall from baseline[6]. A number of factors play role in prophylaxis and management of hypotension which includes counteracting aorto-caval compression by proper positioning, intravenous preloading or co-loading with crystalloids or colloids and vasopressor support[7].

4. Pathophysiology of Hypotension

Normal Pregnant patient is very sensitive to spinal anaesthesia induced hypotension because of an altered balance of vascular tone which is due to following factors:

1. Responses to endogenous pressors, particularly angiotensin II are reduced. This is caused by an endothelium dependent alteration of vascular smooth muscle function.
2. Increased synthesis of vasodilators- prostaglandins and nitric oxide.

As there is no autoregulation, increased dependence on sympathetic vascular tone in normal pregnancy, which will be blocked by intrathecal local anaesthetic, leads to hypotension[8].

Intrathecal injection of local anaesthetic produces sympathetic block which causes

1. Increase in venous capacitance by venodilation and reduces cardiac output.
2. Reduction in systemic vascular resistance[9].
3. Level of block - higher levels as T4 and T5 can inhibit the cardio-accelerator fibres leading to fall in heart rate and hence the cardiac output[10].

5. Adverse Effects of Hypotension

5.1 Maternal

1. Nausea and vomiting: More frequent during spinal anaesthesia for caesarean section than during non obstetric surgery and has multifactorial etiology as following,
    a. Acute hypotension reduces cerebral perfusion, induces transient brainstem ischemia and activates vomiting centre[11].
    b. Spinal anaesthesia decreases splanchnic blood flow resulting splanchnic hypoperfusion releases emetogenic factors such as serotonin from gastrointestinal tract.
    c. Unopposed vagal activity and subsequent hyperactivity of gastrointestinal tract.
2. Dizziness and a sense of impending doom due to cerebral hypoperfusion.
3. Severe hypotension leads to organ ischemia and cardiovascular collapse.

5.2 Fetal

Duration of hypotension is more important than severity. A transient decrease of >30% in blood pressure does not affect neonatal APGAR scores, incidence of meconium stained liquor or the need for oxygen therapy in neonate. Hypotension for less than 2 min does not affect neuro-behavioural outcomes but more than 4 min is associated with neuro-behavioural changes at 4-7 days of life[5]. Uteroplacental hypoperfusion leads to fetal distress which mainly manifest as fetal bradycardia and fetal acidosis[12]. Reduction in uterine blood flow of 60% causes fetal bradycardia and fetal acidosis within 10 min in a previously uncompromised fetus[5].

5.3 Management

As mentioned above, maternal hypotension during caesarean section due to spinal anesthesia is detrimental to both mother and foetus. Immediate treatment with appropriate methods plays an important role in obstetric anaesthesia.

5.4 Non Pharmacological Methods

1. Avoiding aorto-caval compression

In supine position, the gravid uterus of pregnant woman compresses the aorta and the inferior venacava against the bodies of lumbar vertebra leading to decrease in maternal cardiac output and blood pressure, also compromises utero-placental perfusion. It can be prevented by placing

wedge of 12 cm height beneath right buttock which will displace uterus[10].

2. Low dose local anaesthetic agent:

Lowering dose of local anaesthetic reduce incidence of hypotension but it could compromise adequacy of anaesthesia. Hence this may not be optimal technique[13].

3. Mechanical compression device:

Sequential Compression Device (SCD) provides intermittent pressure in sequential manner from ankles upward. Normally SCD moves approximately 125 ml bloods but in parturients SCD moves greater blood volume from periphery to central. SCD reduces incidence and severity of spinal anaesthesia induced hypotension for caesarean section[14].

4. Intravascular Volume Loading Strategies:

Fluid administration during intraoperative period still remains the first line therapy for spinal induced hypotension during caesarean section as there is some degree of dehydration due to preoperative fasting and it helps to maintain cardiac output during onset of spinal blockade.

Maintenance of cardiac output during onset of sympathetic blockade depends on both type and timing of its administration of intravenous fluids.

Fluid loading regimens can be used as follows:

1. Crystalloid preloading
2. Crystalloid co-loading
3. Colloid preloading
4. Colloid co-loading[12]

Comparing all regimens of intravascular fluid loading, least benefits were noted with crystalloid preloading. Considering all above mentioned studies, at present there is no enough evidence to favour any regimen over others. But many studies shown that volume between 500 ml-1000 ml of crystalloid (Ringer`s lactate or normal saline) or colloids can be used to achieve desired hemodynamic goals. Preferably colloids provide more flexibility because both pre-loading and co-loading offer same benefits. But Hydroxy-Ethyl Starches (HES) are more expensive and associated with adverse reactions such as pruritis, alteration in hemostasis and renal failure and sometimes fatal as it has risk of anaphylaxis with incidence of 0.06% but with modern HES these risks are negligible.

Intravascular fluid loading still remains less limited value for prevention and treatment of post-spinal hypotension and should assess the benefits and risk while using these regimens depending on clinical scenarios[12].

5.5 Pharmacological Methods

Vasopressors remain most appropriate approach in prevention and treatment of postspinal hypotension during caesarean delivery.

5.5.1 Metaraminol

Metaraminol is a stereoisomer of meta-hydroxynorepinephrine, potent sympathomimetic, acts as both alpha and beta agonist, used in the management of maternal postspinal hypotension. Prophylactic administration of metaraminol during spinal anaesthesia for caesarean section appears to result in higher umbilical arterial pH levels than doe's phenylephrine. Metaraminol also resulted in a higher umbilical arterial pH, a lower incidence of fetal acidosis, and a lower incidence of nausea or vomiting than did ephedrine. However, metaraminol is associated with a higher incidence of reactive hypertension than was phenylephrine[15].

5.5.2 Methoxamine

Potent sympathomimetic amine that increases both systolic and diastolic blood pressure by acting as pure alpha1 receptor agonist (both alpha 1a and 1b) and no effect on beta receptor. It causes peripheral vasoconstriction and little direct central action[10]. It is devoid of inotrophic and chronotrophic effect and it has been used to counteract the hypotension caused by spinal anaesthesia. Its use has fallen out of favour decades ago owing to concerns regarding decreased uterine blood flow and adverse impact on fetal acid base status[4].

5.5.3 Mephenteramine

It has mixed alpha and beta receptor agonist action with both direct and indirect effect due to release of norepinehrine and epinephrine. Its impact on the heart rate is dependent on the vagal tone. Its use in hypotension after a neuraxial blockade in obstetrics is due to its ability to increase blood pressure by augmenting cardiac output. Disadvantage of mephenteramine is rapid development of tachyphylaxis to its pressor action[4].

5.5.4 Ephedrine

Ephedrine was considered the gold standard vasopressor for decades. It is familiar to most anaesthesiologist, readily available and has a good safety record.

It has both direct alpha and beta agonist actions, but indirect action is more prominent due to release of norepinephrine from sympathetic neurons. It increases blood pressure by beta 1 receptors stimulation by increasing heart rate and cardiac contractility where as the alpha agonist action causes peripheral vasoconstriction[4].

British survey in 2001 found that more than 95% obstetric anaesthetist in UK, used ephedrine as the sole vasopressor, with only 0.4% choosing phenylephrine. Many studies have been done to investigate the role of prophylactic ephedrine for prevention of maternal hypotension.

Many studies showed in elective caesarean deliveries giving ephedrine resulted in more incidence of fetal acidosis. In key study by Ngan Kee *et al.*[16], the authors performed umbilical artery blood gas analysis they showed a significant decrease in pH, base excess and oxygen content as well as increase in paCO2 if the parturient had received large doses of ephedrine.

It is also important to note that in all newborns in the study, none of the APGAR score at one and five minutes was less than 7&9 respectively. These results can be explained by maximum placental transfer of ephedrine and possibly by a foetal beta adrenergic stimulating effect of ephedrine as evident by high serum lactate, glucose and epinephrine levels in newborn of mothers who had received ephedrine[12].

Ephedrine and phenylephrine are commonly used to prevent and treat spinal hypotension. There are many studies which compared the use of ephedrine versus phenylephrine for prevention of hypotension in obstetric patients.

Vesser *et al*. performed an updated meta-analysis of studies that compared phenylephrine and ephedrine. Results from 20 trials, including 1069 patients showed that the risk ratio for foetal acidosis (umbilical artery pH less than 7.2) was 5.29 [95% Confidence Interval (CI) 1.62-17.25] for ephedrine versus phenylephrine[15].

Dyer and Biccard commented that adverse neonatal outcome including mortality is associated with low fetal pH. It is also stated that phenylephrine more appropriately counters the physiological changes induced by spinal anaesthesia and delayed pressure response of ephedrine may contribute to a higher incidence of nausea, vomiting[15].

Ephedrine, with its longer duration of action still has a role in obstetric anaesthesia in preventing or treating spinal induced hypotension when given in an appropriate dose.

The optimal method of administrating ephedrine (alone or combined with vasopressor) awaits future study.

5.5.5 Phenylephrine

Phenylephrine is considered "first line vasopressor" in the obstetric anesthesia.

Studies over last twenty five years have not only proved the safety of phenylephrine, but also demonstrated its increasing effectiveness in preventing maternal hypotension and its side effects and lower risk of fetal acidosis[1].

Phenylephrine is a pure alpha adrenergic agonist with no beta adrenergic activity. It has faster onset of action, easier to titrate and associated with improved fetal pH. It induces arteriolar vasoconstriction to increase systemic vascular resistance and mean arterial pressure, thus leading to reflex decrease in heart rate and in turn cardiac output[16]. Because of these properties, it was mistakenly thought to compromise uteroplacental circulation which was contradicted by the initial study conducted by Ramanathan *et al.*[17]. who concluded that Phenylephrine did not cause fetal acidosis when used to treat maternal hypotension[17]. As phenylephrine continued to gain evidence, some authors questioned the usage of ephedrine as first line vasopressor.

As of now, most of the current guidelines consider phenylephrine as the first preferred vasopressor in treating obstetric hypotension following spinal anesthesia in routine caesarean section patients, but also recommend use of both ephedrine and phenylephrine as per clinical situations, as both are considered equally efficacious[5].

While most of phenylephrine studies involve healthy parturients, impact of its use in some clinical situations like compromised uteroplacental circulation, pre eclampsia, cardiac disease is unclear.

Even though evidence is emerging slowly[18] further studies are required to prove its safety in high-risk pregnancies[18].

There is also lot of confusion regarding the usage of phenylephrine regarding its optimal dosage, timing (prophylactic or reactive) and method of administration

(bolus or continous infusion). Even though studies have found ED95 of phenylephrine as: 122 mcg (Tanaka *et al.*)[19], 144 mcg (George *et al.,* 2010)[20], 50-100 mcg dose is commonly used in clinical practice[21].

Infusions of phenylephrine are always associated with greater hemodynamic stability and less maternal adverse effects than bolus dosing[22] even though there is added task of preparing an infusion and setting a syringe pump. However prophylactic fixed rate infusions may not have much advantage in clinical practice[20] while prophylactic variable phenylephrine infusions with rescue boluses maintain better maternal blood pressure[23].

Research is continuing with phenylephrine regarding better method of administration. A study with closed loop double vasopressor automated system showed better control of maternal blood pressure and no reactive hypertension compared to manual bolus vasopressor. Bradycardia and decrease in cardiac output with phenylephrine has lead to search for better alternatives with Nor epinephrine being tried as a vasopressor for treating obstetric spinal hypotension[24,25].

5.5.6 Nor Epinephrine

Norepinephrine has potent alpha-1 adrenergic agonist and comparatively modest beta agonist activity. It causes marked vasoconstriction with some direct inotropic effects[1] with its mild beta adrenergic activity it has less depressant effect on heart rate and cardiac output. But many anaesthesiologists are questioning use of such potent agent in non intensive setup.

Nevertheless, various authors have studied the efficacy of Norepinephrine in treating maternal hypotension following spinal anesthesia[26]. A metaanalysis has shown neither similar efficacy of nor epinephrine as phenylephrine in managing maternal hypotension[27] with decreased incidence of side effects like bradycardia and Intraoperative nausea and vomiting[28]. Further studies on norepinephrine are required to evaluate its feasibility in obstetric scenario before it can be used as a routine vasopressor.

Looking forward to future, automated computer controlled systems with multiple vasopressors have to be further evaluated and concurrent advances in non invasive cardiac output monitoring in obstetric patients might help us in achieving better hemodynamic profile.

6. Conclusion

Spinal anaesthesia is the standard technique in many countries for caesarean section as it provides excellent operating conditions and is well tolerated. Hypotension is a common problem and can result in unpleasant symptoms in mother and harm the foetus.

Lot of studies and clinical trials have been conducted and guidelines have been published for the management of maternal hypotension. Ephedrine and phenylephrine are commonly used drugs to obviate hypotension. In the past, ephedrine was considered as the appropriate vasopressor agent for most pregnant patients. Now, with new clinical trials, its use has reduced and has been moved down to a second line agent. Phenylephrine, on the other hand, has emerged as a reliable and fast agent for treatment of hypotension. Recent investigation and analysis continues to support the use of phenylephrine over ephedrine. New clinical studies are showing that low dose norepinephrine is an effective alternative to phenylephrine with the advantage of less depression of maternal heart rate and cardiac output. More research is required in this subject.

The cardiac output monitoring to guide fluid and vasopressor use during spinal anaesthesia for caesarean section is likely to become more popular in future.

The use of smart pumps and multidrug vasopressor infusion can prove more beneficial to have greater cardiovascular stability.

7. References

1. Campbell JP, Stocks GM. Management of hypotension with vasopressors at caesarean section under spinal anaesthesia-have we found the Holy Grail of obstetric anaesthesia? Anaesthesia, 2018; 73(1):3-6. https://doi.org/10.1111/anae.14114. PMid:29090732.
2. Mohamed AA, Safan TF. Nor-epinephrine versus vasopressin infusion for prevention of spinal-induced hypotension: a placebo-controlled study. Southern African Journal of Anaesthesia and Analgesia, 2017; 23(4):96-101. https://doi.org/10.1080/22201181.2017.1338333.
3. Macarthur A, Riley ET. Obstetric anesthesia controversies: Vasopressor choice for postspinal hypotension during cesarean delivery. International Anesthesiology Clinics, 2007; 45(1):115-132. https://doi.org/10.1097/AIA.0b013e31802b8d53. PMid:17215703.

4. Nag DS, Samaddar DP, Chatterjee A, Kumar H, Dembla A. Vasopressors in obstetric anesthesia: A current perspective. World J. Clin. Cases, 2015; 3(1):58-64. https://doi.org/10.12998/wjcc.v3.i1.58. PMid:25610851 PMCid:PMC4295220
5. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, Palanisamy A, Sia AT, Van de Velde M, Vercueil A. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Obstetric Anesthesia Digest, 2018; 38(4):171-172. https://doi.org/10.1097/01.aoa.0000547270.12467.06.
6. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's Anesthesia E-Book. Elsevier Health Sciences, 8th Edition; 2014. p. 1713.
7. Hughes SC, Levinson G, Rosen MA, Shnider SM. Anesthesia for Obstetrics, Shnider and Levinson's Editors, 5th Edition, Lippincott Williams & Wilkins; 2013. p.192 .
8. Sharwood-Smith G, Drummond GB. Hypotension in obstetric spinal anaesthesia: A lesson from pre-eclampsia. British Journal of Anaesthesia, 2009; 102(3):291-294. https://doi.org/10.1093/bja/aep003. PMid:19218369.
9. Barash P, Cullen BF, Stoelting RK, Cahalan M, Stock MC, Ortega R. Handbook of Clinical Anesthesia. Lippincott Williams & Wilkins; 12th May 2017. p. 935.
10. Mitra JK, Roy J, Bhattacharyya P, Yunus M, Lyngdoh NM. Changing trends in the management of hypotension following spinal anesthesia in cesarean section. Journal of Postgraduate Medicine, 2013; 59(2):121. http://www.jpgmonline.com/text.asp?2013/59/2/121/113840. PMid:23793313.
11. Hirose N, Kondo Y, Maeda T, Suzuki T, Yoshino A. Relationship between regional cerebral blood volume and oxygenation and blood pressure during spinal anesthesia in women undergoing cesarean section. Journal of Anesthesia, 2016; 30(4):603-609. https://doi.org/10.1007/s00540-016-2165-6. PMid:27011334.
12. Loubert C. Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: Continuing professional development. Canadian Journal of Anesthesia/Journal Canadien D'anesthésie, 2012; 59(6):604-619. https://doi.org/10.1007/s12630-012-9705-9. PMid:22528166.
13. Roofthooft E, Van de Velde M. Low-dose spinal anaesthesia for Caesarean section to prevent spinal-induced hypotension. Current Opinion in Anesthesiology, 2008; 21(3):259-262. https://doi.org/10.1097/ACO.0b013e3282ff5e41. PMid:18458538.
14. Sujata N, Arora D, Panigrahi BP, Hanjoora VM. A sequential compression mechanical pump to prevent hypotension during elective cesarean section under spinal anesthesia. Int. J. Obstet. Anesth., 2012; 21(3):140-145 https://doi.org/10.1016/j.ijoa.2012.01.003. PMid:22398360.
15. Chao E, Sun HL, Huang SW, Liao JH, Ma PL, Chen HC. Metaraminol use during spinal anaesthesia for caesarean section: a meta-analysis of randomised controlled trials. International Journal of Obstetric Anesthesia. 2019. https://doi.org/10.1016/j.ijoa.2019.01.009. PMid:30772119.
16. Wang X, Shen X, Liu S, Yang J, Xu S. The efficacy and safety of norepinephrine and its feasibility as a replacement for phenylephrine to manage maternal hypotension during elective cesarean delivery under spinal anesthesia. BioMed Research International, 2018 dec 31; p. 1869189. https://doi.org/10.1155/2018/1869189. PMid:30687737 PMCid:PMC6330831.
17. Ramanathan S, Grant GJ. Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiologica Scandinavica, 1988; 32(7):559-565. https://doi.org/10.1111/j.1399-6576.1988.tb02786.x. PMid:3188826.
18. Ngan Kee WD, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section. Anaesthesia, 2008 Dec; 63(12):1319-1326. https://doi.org/10.1111/j.1365-2044.2008.05635.x. PMid:19032300.
19. Tanaka M, Balki M, Parkes RK, Carvalho JC. ED95 of phenylephrine to prevent spinal-induced hypotension and/or nausea at elective cesarean delivery. International Journal of Obstetric Anesthesia. 2009; 18(2):125-130. https://doi.org/10.1016/j.ijoa.2008.09.008. PMid:19162468.
20. George RB, McKeen D, Columb MO, Habib AS. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. Anesthesia and Analgesia, 2010; 110(1):154-158. https://doi.org/10.1213/ANE.0b013e3181c30b72. PMid:19910625.
21. Habib AS. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. Anesthesia and Analgesia, 2012; 114(2):377-390. https://doi.org/10.1213/ANE.0b013e3182373a3e. PMid:22104076.

22. George RB, McKeen DM, Dominguez JE, Allen TK, Doyle PA, Habib AS. A randomized trial of phenylephrine infusion versus bolus dosing for nausea and vomiting during Cesarean delivery in obese women. Canadian Journal of Anesthesia, 2018; 65(3):254-262. https://doi.org/10.1007/s12630-017-1034-6. https://doi.org/10.1007/s12630-017-1034-6. PMid:29209926 PMCid:PMC5856192.
23. Allen TK, George RB, White WD, Muir HA, Habib AS. A double-blind, placebo-controlled trial of four fixed rate infusion regimens of phenylephrine for hemodynamic support during spinal anesthesia for cesarean delivery. Anesthesia and Analgesia, 2010; 111(5):1221-1229. https://doi.org/10.1213/ANE.0b013e3181e1db21. PMid:20495139.
24. Siddik-Sayyid SM, Taha SK, Kanazi GE, Aouad MT. A randomized controlled trial of variable rate phenylephrine infusion with rescue phenylephrine boluses versus rescue boluses alone on physician interventions during spinal anesthesia for elective cesarean delivery. Anesthesia and Analgesia, 2014; 118(3):611-618. https://doi.org/10.1213/01.ane.0000437731.60260.ce. PMid:24299932.
25. Sng BL, Tan HS, Sia AT. Closed-loop double-vasopressor automated system vs manual bolus vasopressor to treat hypotension during spinal anaesthesia for caesarean section: A randomised controlled trial. Anaesthesia, 2014; 69(1):37-45. https://doi.org/10.1111/anae.12460. PMid:24256483.
26. Vallejo MC, Attaallah AF, Elzamzamy OM, Cifarelli DT, Phelps AL, Hobbs GR, Shapiro RE, Ranganathan P. An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. International Journal of Obstetric anesthesia, 2017; 29:18-25. https://doi.org/10.1016/j.ijoa.2016.08.005. PMid:27720613.
27. Onwochei DN, Kee N, Warwick D, Fung L, Downey K, Ye XY, Carvalho JC. Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: A sequential allocation dose-finding study. Anesthesia and Analgesia, 2017; 125(1):212-218. https://doi.org/10.1213/ANE.0000000000001846. PMid:28248702.
28. Xu S, Shen X, Liu S, Yang J, Wang X. Efficacy and safety of norepinephrine versus phenylephrine for the management of maternal hypotension during cesarean delivery with spinal anesthesia: A systematic review and meta-analysis. Medicine, 2019; 98(5):e14331. https://dx.doi.org/10.1097%2FMD.0000000000014331. PMID: 30702617. PMCid:PMC6380847.