South Afr J Anaesth Analg. 2024;30(4):106-110
https://doi.org/10.36303/SAJAA.3140

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

ORIGINAL RESEARCH

The role of adrenaline in the management of obstetric spinal hypotension during caesarean section: a systematic review

F Thejane,[1] D Bishop,[1] R Rodseth[1,2]

[1] Discipline of Anaesthesiology and Critical Care, School of Clinical Medicine, University of KwaZulu-Natal, South Africa
[2] Netcare Limited, South Africa
Corresponding author, email: *fumanethejane@yahoo.com; thejanefumane@gmail.com*

Background: Obstetric spinal hypotension is a common complication. After considerable research, phenylephrine infusion has been established as the first-line agent for its management. Adrenaline is sometimes recommended for use when phenylephrine is unavailable in low-resource settings; however, little research informs this recommendation.

Methods: We conducted a systematic review of all randomised controlled trials comparing adrenaline to other vasoconstrictors for the management of spinal hypotension during caesarean section. Primary study outcomes were the incidence of maternal hypotension and fetal acidosis. Secondary outcomes were maternal bradycardia, tachycardia, nausea, vomiting, hypertension, requirement for cardiac resuscitation, loss of consciousness, and Apgar scores.

Results: Participants were 20–40 years of age, American Society of Anesthesiologists (ASA) grade I–II, undergoing elective caesarean section. Of 1 935 publications identified, six were extracted for full-text review, of which three were included in the final data synthesis. There was significant heterogeneity between studies, and only one was of high quality, which precluded meta-analysis. Comparator vasoconstrictors included ephedrine, phenylephrine, and noradrenaline, administered either by bolus or infusion.

Primary outcomes: adrenaline did not result in an absolute blood pressure difference when compared to the other agents. One study reported a lower mean venous cord bicarbonate level, and a second reported a lower base excess in the adrenaline group.

Secondary outcomes: compared to ephedrine, adrenaline resulted in a lower heart rate. Compared to phenylephrine and noradrenaline, adrenaline had a lower and a similar incidence of bradycardia, respectively. There were no between-group differences in the other secondary outcomes.

Conclusion: Small trials provided limited support for the efficacy and safety of adrenaline in the management of obstetric spinal hypotension. However, there is insufficient evidence to inform recommendations for the use of this vasopressor. Therefore, the use of adrenaline should be limited to situations where phenylephrine, supplemented as necessary by less potent agents, is unavailable. In view of the proven safety and efficacy of phenylephrine, ethical justification for further research on adrenaline could be questioned.

Keywords: adrenaline, obstetrics, caesarean section, obstetric spinal hypotension, neuraxial anaesthesia

Introduction

Obstetric spinal hypotension is a common anaesthetic problem with important attendant maternal outcomes.[1] In South Africa, hypotension prior to delivery of the baby was a major morbidity in 25% of maternal deaths.[2] Traditionally, pharmacological management of obstetric spinal hypotension has been focused on the use of ephedrine. Over the last two decades, there has been a significant shift to the use of phenylephrine infusions as the preferred method of prevention and treatment.[3]

Research into the pharmacological management of obstetric spinal hypotension is dominated by these traditional first-line agents, with minimal evidence supporting the use of adrenaline. As a World Health Organization (WHO) essential drug, adrenaline is almost universally available, even where other drugs are unavailable, and clinicians are familiar with its use. This systematic review seeks to identify randomised controlled trials comparing the use of adrenaline with other vasoconstrictors for the management of obstetric spinal hypotension.

Methodology

We aimed to conduct a systematic review and meta-analysis according to the Cochrane Handbook and reported our findings per the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[4,5] The study protocol was registered with PROSPERO, an international prospective register of systematic reviews (CRD42022364586).

Eligibility criteria

All randomised controlled trials comparing the use of adrenaline to a vasoconstrictor for the management of obstetric spinal anaesthesia-induced hypotension in women having urgent or elective caesarean section were considered eligible for inclusion in the systematic review.

Information sources and search strategy

On 8 November 2022, we searched the following electronic databases: PubMed, Embase, CT.gov, ICTRP, CINAHL, and The

Cochrane Library. We also searched our own files, consulted with experts, reviewed reference lists from identified articles, and searched for cited references of key publications. The following combination of keywords and medical subject headings (MeSH) terms were used: ("epinephrine" OR "adrenaline") AND (("obstetric anesthesia OR cesarean section OR cesarean delivery") AND ("spinal anesthesia") AND ("maternal hypotension OR maternal hemodynamic"))). This search was updated on 29 June 2023.

Eligibility assessment

In duplicate we screened titles and abstracts of each identified citation. Those reports possibly meeting the eligibility criteria were extracted for full review.

Outcomes of interest

The primary study outcomes were the incidence of maternal hypotension and fetal acidosis. Secondary outcomes included the incidence of maternal bradycardia, tachycardia, nausea, vomiting, hypertension, requirement for cardiac resuscitation, maternal loss of consciousness, and Apgar scores.

Quality and risk of bias analysis

We assessed the risk of bias of each study using the Cochrane Collaboration risk of bias table. The quality of the included studies was evaluated using the grading of recommendations, assessment, development, and evaluation (GRADE) quality assessment checklist, which takes into account the risk of bias, inconsistencies, indirectness, imprecision, and reporting bias.

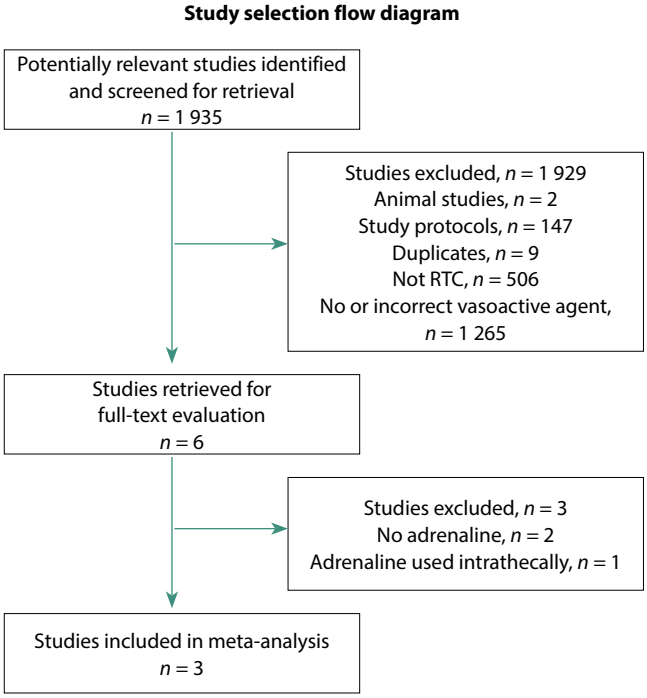

Figure 1: Study selection flow diagram to identify randomised controlled trials comparing adrenaline to other vasoconstrictors for the management of obstetric spinal hypotension during caesarean section
RCT – randomised controlled trial

Statistical analysis

The systematic review was conducted using Review Manager (RevMan) version 5.4 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[6] Heterogeneity between studies was assessed using univariate chi-square analysis and I^2. Results were reported as odds ratios (OR), with 95% confidence intervals (CI), and presented as forest plots. Random effects models would have been used where the I^2 statistic was found to be > 25% (representing significant heterogeneity); otherwise, a fixed effects model was used.

Results

Trial selection

The electronic database search strategy identified 1 935 publications. From these, six publications were extracted for full-text review, of which three were included in the final data synthesis (Figure 1).[7-12] The low number of eligible trials, together with differences in reporting of outcomes, precluded meta-analysis.

Trial characteristics, outcomes and quality

The three trials included women between 20 and 40 years of age, ASA I–II, undergoing elective caesarean section, with trial participant numbers ranging from 80 to 160.[10-12] Further trial characteristics are detailed in Table I. The three trials used different comparator vasoconstrictors. Moradi et al.[10] compared adrenaline to ephedrine, Wang et al.[11] adrenaline to phenylephrine, and Biricik et al.[12] adrenaline to phenylephrine, noradrenaline, and saline placebo. Table II provides details of the methods of administration of these medications.

Two of the three trials included blood pressure changes as part of their primary trial outcomes.[10,12] Maternal bradycardia was the primary outcome for Wang et al.[11] Primary, secondary, and adverse outcomes for each of the trials are detailed in Table III.

Trial quality was high for Biricik et al., high to uncertain for Wang et al., and uncertain to low for Moradi et al. Trial quality details are provided in the appendix in supplementary Figures S1 and S2.[10-12]

Trial outcomes

This analysis sought to compare the use of adrenaline with other vasoconstrictors for the management of obstetric spinal hypotension. In view of the low number of studies eligible for inclusion, a summary of the results is therefore presented by specific outcomes.

Effect on blood pressure

Moradi et al. reported the difference in systolic and diastolic blood pressure at baseline, and then every two minutes between the adrenaline and ephedrine groups.[10] Mean systolic blood pressure was significantly lower in the adrenaline group than the ephedrine group between eight and 16 minutes from baseline ($p < 0.05$). Mean diastolic blood pressure was significantly lower

Table I: Characteristics of included randomised controlled trials comparing adrenaline to other vasoconstrictors for the management of spinal hypotension during caesarean section

Author, year	Comparator drugs	Caesarean degree of urgency	Patients (n)	Age in years (mean [standard deviation] or range)	Gestational age in the singleton pregnancies studied (mean [standard deviation] or range)
Moradi, 2021[10]	Adrenaline, ephedrine	Elective	126	20–40	36–40 weeks
Wang, 2020[11]	Adrenaline, phenylephrine	Elective	80 (40 per group)	27 (3.5)	40 weeks (1)
Biricik, 2020[12]	Adrenaline, phenylephrine, noradrenaline, saline	Elective and emergency	160 (40 per group)	31.1 (5.4)	Not reported

Table II: Trial design characteristics of included randomised controlled trials comparing adrenaline to other vasoconstrictors for the management of spinal hypotension during caesarean section

Author, year	Adrenaline dose	Comparator vasoconstrictor	Dosing adjustment triggers	Intervention if BP targets were not met by vasoconstrictor
Moradi, 2021[10]	4 µg bolus	Ephedrine: 10 mg bolus	Bolus if SBP < 20% of baseline or SBP < 100 mmHg	
Wang, 2020[11]	4 µg/ml at 0.1 µg/kg/min	Phenylephrine: 40 µg/ml at 1 µg/kg/min	Increased to maintain SBP > 90% of baseline Stopped if SBP > 120% of baseline or > 140 mmHg	SBP < 80 mmHg or < 80% of baseline, phenylephrine 40 µg or adrenaline 4 µg HR < 50 bpm, atropine 0.5 mg
Biricik, 2020[12]	5 µg/ml 30 ml/h, fixed-rate	Noradrenaline: 5 µg/ml Phenylephrine: 100 µg/ml	30 ml/h, fixed-rate 30 ml/h, fixed-rate	SBP < 80% of baseline, 5 mg ephedrine bolus

BP – blood pressure, bpm – beats per minute, HR – heart rate, SBP – systolic blood pressure

Table III: Trial outcome measures for included randomised controlled trials comparing adrenaline to other vasoconstrictors for the management of spinal hypotension during caesarean section

Author, year	Primary outcome	Secondary outcomes	Adverse events assessed
Moradi, 2021[10]	Difference in mean SBP and heart rate	Difference in mean diastolic blood pressure Differences in mean umbilical venous pH, pCO_2, pO_2, and bicarbonate Apgar score at one and five minutes	None noted
Wang, 2020[11]	Incidence of maternal bradycardia before delivery	Umbilical artery pH	Hypotension Nausea Vomiting
Biricik, 2020[12]	Incidence of hypotension (SBP < 80% of baseline)	Use of rescue ephedrine (count) Mean ephedrine consumption Apgar score at one and five minutes Umbilical venous pH	Bradycardia Hypertension Nausea Vomiting

SBP – systolic blood pressure, pCO_2 – partial pressure of carbon dioxide, pO_2 – partial pressure of oxygen

in the adrenaline group than the ephedrine group from eight to 45 minutes after the baseline reading ($p < 0.05$). The largest absolute difference between the adrenaline and ephedrine groups was 9.4 mmHg (103.1 vs. 112.5 mmHg) for the systolic and 6.4 mmHg (52.8 vs. 59.2 mmHg) for the diastolic blood pressure. Wang et al.[11] reported higher systolic blood pressure, diastolic blood pressure, heart rate, and cardiac output at the times of skin incision and delivery in the adrenaline group than the phenylephrine group.

Both Biricik et al. and Wang et al. reported the incidence of hypotension.[11,12] In the former study, there was no significant difference in the incidence of hypotension between the adrenaline (72.5%, n = 29/40), phenylephrine (67.5%, n = 27/40), and noradrenaline (70%, n = 28/40) groups (p = 0.228). Similarly, in the latter investigation, there was no difference in the incidence of hypotension between the adrenaline and phenylephrine groups (2.5%, n = 1/40 vs. 7.5%, n = 3/40; p = 0.36). In addition, Biricik et al. reported no difference in the mean (standard deviation [SD]) number of episodes of hypotension between the adrenaline (3.2 [SD 4.2]), phenylephrine (2.88 [3.6]), and noradrenaline (3.5 [4.4]) groups (p = 0.228).[12]

In summary, Moradi et al. reported a lower systolic and diastolic blood pressure when comparing adrenaline to ephedrine, when using an absolute blood pressure threshold to define hypotension.[10] There were no differences between adrenaline, phenylephrine, and noradrenaline.

Heart rate

Moradi et al. reported the difference from baseline in mean heart rate between the two groups, every two minutes until 20 minutes, and then every five minutes until 45 minutes.[10] The mean heart rate was lower in the adrenaline than the ephedrine group at minutes 10, 25, 35, and 45 ($p < 0.05$).

Wang et al. reported a lower incidence of bradycardia in the adrenaline than the phenylephrine group (5%, *n* = 2/40 vs. 22.5%, *n* = 9/40; *p* = 0.02).[11] Biricik et al. reported no difference in bradycardia incidence between the adrenaline (7.5%, *n* = 4/40), phenylephrine (15%, *n* = 6/40), and noradrenaline group (12.5%, *n* = 5/40; *p* = 0.752).[12]

Nausea and vomiting

Biricik et al. reported that the adrenaline group had an incidence of nausea and vomiting of 12.5% (*n* = 5/40) and 5% (*n* = 2/40), respectively in the adrenaline group 12.5% (*n* = 5/40), 7.5% (*n* = 3/40) in the phenylephrine group, and 17.5% (*n* = 7/40) and 8% (*n* = 3/40) in the noradrenaline group.[12] There was no statistically significant difference between these groups for either nausea (*p* = 0.734) or vomiting (*p* = 0.452). Wang et al. reported a composite nausea and vomiting outcome of 2.5% (*n* = 1/40) in the adrenaline group and 5% (*n* = 2/40) in the phenylephrine group (*p* = 0.71).[11]

Apgar scores

Moradi et al. showed no significant between-group difference in Apgar score at one and five minutes (*p* = 0.204).[10] Biricik et al. reported median (interquartile range [IQR]) Apgar scores ≥ 8 (1) at one minute and ≥ 9 (1) at five minutes for the adrenaline, phenylephrine, and noradrenaline groups.[12] Wang et al. reported mean (SD) Apgar scores ≥ 9 (1) at one and five minutes, and all scores > 7, for both the adrenaline and phenylephrine groups.[11]

Cord blood analysis

Moradi et al. found no significant between-group difference in mean (SD) venous cord blood pH (adrenaline 7.33 [0.07] vs. ephedrine 7.32 [0.05]; *p* = 0.374).[10] The median pH of the venous cord blood for Biricik et al. was 7.32 (IQR 0.05) in the adrenaline group, 7.31 (IQR 0.03) in the phenylephrine group, and 7.34 (IQR 0.06) in the noradrenaline group.[12] Wang et al. found no neonates with a pH < 7.2 and no significant between-group difference in mean (SD) pH between the groups (adrenaline 7.38 [0.06] vs. phenylephrine 7.36 [0.07]; *p* = 0.17).[11]

Moradi et al. found that the adrenaline group had a lower mean (SD) bicarbonate (22.43 [3.69] mmol/L) compared to the ephedrine group (24.6 [6.89] mmol/L; *p* = 0.004).[10] Similarly, Biricik et al. found significant differences between median (IQR) base excess measurements across all three groups (adrenaline -3.35 mmol/L [4.48], phenylephrine -4.3 mmol/L [1.28], noradrenaline -1.25 mmol/L [3.75]; *p* = 0.001).[12] Wang et al. found no significant between-group difference in mean (SD) base excess (adrenaline -2.3 [0.6] mmol/L vs. phenylephrine -2.5 [0.7] mmol/L; *p* = 0.18).[11]

Maternal loss of consciousness and cardiac resuscitation

There were no instances of these outcomes in any of the three trials.

Discussion

This systematic review sought to compare adrenaline to other vasopressors for the management of obstetric spinal hypotension. Despite adrenaline being a WHO essential drug, we were only able to identify three randomised controlled trials that fulfilled study eligibility. Of these three, only one was of high quality. Recently published meta-analyses examining prophylactic noradrenaline and phenylephrine in spinal anaesthesia for caesarean section have, on average, identified 10 or more high-quality studies eligible for study inclusion.[13-15] Moreover, a Bayesian network meta-analysis of all vasopressor drugs published in 2020 identified 52 randomised controlled trials, of which none studied adrenaline.[16] This paucity of research is concerning when considering the morbidity associated with obstetric spinal hypotension in areas where first-line agents are unavailable.

An international consensus guideline published in 2018 makes recommendations regarding the choice of vasopressor and the mode of administration.[3] Phenylephrine is considered the agent of choice, and infusions are recommended for prophylaxis of obstetric spinal hypotension. Other vasopressors, such as noradrenaline, ephedrine, and metaraminol, are also discussed. Adrenaline is only recommended for circulatory collapse, or in resource-limited settings where alternatives are not available. Bolus doses of 10 µg are suggested, and prophylactic adrenaline infusions are not discussed. As shown in this review, there is little high-quality evidence to inform recommendations.

In this analysis, the included trials compared adrenaline to ephedrine in two cases, phenylephrine in two cases, and noradrenaline in one case. Moradi et al. compared adrenaline boluses to ephedrine boluses.[10] This is probably not an ideal approach considering the pharmacokinetics of adrenaline, and this was reflected in the trial, where lower mean and diastolic blood pressures were shown in the adrenaline group compared to the ephedrine group. The other two trials used adrenaline infusions. Wang et al. adjusted the infusions according to the blood pressure of the patient, while Biricik et al. maintained a fixed infusion rate.[11-12] This is a low-complexity approach that could be useful when inexperienced medical staff are doing a caesarean section, and has been similarly described with low-dose, fixed-rate phenylephrine infusions.[17] Both of these trials found no difference in the incidence of hypotension when using adrenaline compared to ephedrine. Wang et al. reported an increased heart rate in the adrenaline group as well as a lower incidence of bradycardia compared to phenylephrine.[11]

Adrenaline increases lactate production by stimulating glycolysis and pyruvate generation. The impact upon neonatal outcome is not clear. In all three trials, venous cord blood pH in the adrenaline group was not significantly different from comparators. However, Moradi et al. found that the adrenaline group had lower mean bicarbonate measurements compared to the ephedrine group.[10] When compared to phenylephrine, the adrenaline groups had similar base excess measurements, but these were lower than in the noradrenaline group. It is difficult to draw definitive conclusions based on this data.

The heterogeneity of the comparator agents and the trial outcome definitions, coupled with the small number of studies identified, precluded meta-analysis, and reliable conclusions about the safety and efficacy of adrenaline cannot be drawn. Ideally, it could be of value to patient care to compare adrenaline infusions to ephedrine bolus strategies, or to the use of phenylephrine administered by bolus or infusion strategies, in areas where first-line vasopressors are unavailable. These studies would have to be high-quality trials with clearly defined outcomes that would allow meaningful inclusion in meta-analyses. However, the ethical aspects of conducting trials on a powerful vasopressor when proven, established first-line alternatives are available, are complex. A further concern is the safety of running dilute adrenaline infusions through a peripheral intravenous line, although studies suggest the incidence of adverse events is low.[18]

Limitations of our systematic review included the very few studies included, precluding meta-analysis. There was also significant heterogeneity in study methodology and trial outcomes, and mixed trial quality. Overall study sizes were also small, especially in comparison to the volume of work that has been done with other vasopressors.

Conclusion

Small trials provided limited support for the efficacy and safety of adrenaline in the management of obstetric spinal hypotension. However, there is insufficient evidence to inform recommendations for the use of this vasopressor. Therefore, the use of adrenaline should be limited to situations where phenylephrine, supplemented as necessary by less potent agents, is unavailable. In view of the proven safety and efficacy of phenylephrine, ethical justification for further research on adrenaline could be questioned.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

Approval was obtained from the University of Kwazulu-Natal Biomedical Research Ethics Committee (BREC/00004523/2022).

ORCID

F Thejane https://orcid.org/0009-0008-1993-9241
D Bishop https://orcid.org/0000-0001-9861-3646
R Rodseth https://orcid.org/0000-0002-3779-7805

References

1. Bishop DG, Rodseth RN, Dyer RA. Recipes for obstetric spinal hypotension: the clinical context counts. S Afr Med J. 2016;106(9):861-4. https://doi.org/10.7196/SAMJ.2016.v106i9.10877.
2. Lundgren AC. Trends in maternal deaths associated with anaesthesia in the triennium 2017-2019. O&G Forum. 2020;30(4):46-7.
3. Kinsella SM, Carvalho B, Dyer RA, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia. 2018;73(1):71-92. https://doi.org/10.1111/anae.14080.
4. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Available from: www.handbook.cochrane.org2011.
5. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1). https://doi.org/10.1186/2046-4053-4-1.
6. Cochrane. Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre; 2014.
7. Bhardwaj N, Jain K, Arora S, Bharti N. A comparison of three vasopressors for tight control of maternal blood pressure during cesarean section under spinal anesthesia: effect on maternal and fetal outcome. J Anaesthesiol Clin Pharmacol. 2013;29(1):26-31. https://doi.org/10.4103/0970-9185.105789.
8. Eskandr AM, Ahmed AM, Bahgat NME. Comparative study among ephedrine, norepinephrine and phenylephrine infusions to prevent spinal hypotension during cesarean section. A randomized controlled double-blind study. Egypt J Anaesth. 2021;37(1):295-301. https://doi.org/10.1080/11101849.2021.1936841.
9. Hamzei A, Nazemi SH, Alami A, Gochan ADM, Kazemi A. Comparing different epinephrine concentrations for spinal anesthesia in cesarean section: a double-blind randomized clinical trial. Iran J Med Sci. 2015;40(4):302-8.
10. Moradi F, Pouryaghobi SM, Rezaee M, et al. Comparison of the effect of intravenous epinephrine and ephedrine in the management of hypotension and bradycardia during cesarean section under spinal anesthesia in Kamali Hospital, Karaj. Venezuelan Arch Pharm Ther. 2021;40(2). http://doi.org/10.5281/zenodo.4710978.
11. Wang YB, Yang ZY, Zhang WP. Comparison of continuous infusion of epinephrine and phenylephrine on hemodynamics during spinal anesthesia for cesarean delivery: a randomized controlled trial. Clin Ther. 2020;42(10):2001-9. https://doi.org/10.1016/j.clinthera.2020.08.004.
12. Biricik E, Karacaer F, Ünal İ, Sucu M, Ünlügenç H. The effect of epinephrine for the treatment of spinal-hypotension: comparison with norepinephrine and phenylephrine, clinical trial. Braz J Anesthesiol (English Edition). 2020;70(5):500-7. https://doi.org/10.1016/j.bjane.2020.08.002.
13. Liu P, He H, Zhang S-S, et al. Comparative efficacy and safety of prophylactic norepinephrine and phenylephrine in spinal anesthesia for cesarean section: a systematic review and meta-analysis with trial sequential analysis. Front Pharmacol. 2022;13:1015325. https://doi.org/10.3389/fphar.2022.1015325.
14. Li Y, Shuai B, Huang H. Prophylactic intravenous norepinephrine for the prevention of hypotension during spinal anesthesia for elective cesarean section: a systematic review and dose-response meta-analysis of randomized controlled trials. Front Pharmacol. 2023;14:1247214. https://doi.org/10.3389/fphar.2023.1247214.
15. Heesen M, Hilber N, Rijs K, et al. A systematic review of phenylephrine vs. noradrenaline for the management of hypotension associated with neuraxial anaesthesia in women undergoing caesarean section. Anaesthesia. 2020;75(6):800-8. https://doi.org/10.1111/anae.14976.
16. Singh PM, Singh NP, Reschke M, et al. Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes. Br J Anaesth. 2020;124(3):e95-107. https://doi.org/10.1016/j.bja.2019.09.045.
17. Bishop DG, Cairns C, Grobbelaar M, Rodseth RN. Prophylactic phenylephrine infusions to reduce severe spinal anesthesia hypotension during cesarean delivery in a resource-constrained environment. Anesth Analg. 2017;125(3):904-6. https://doi.org/10.1213/ANE.0000000000001905.
18. Owen VS, Rosgen BK, Cherak SJ, et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. Crit Care. 2021;25(146). https://doi.org/10.1186/s13054-021-03553-1.

Appendix available online