Predictive ability of pulse oximetry-derived indices for hypotension after spinal anaesthesia for caesarean section: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction In general, caesarean sections are performed under spinal anaesthesia. Hypotension after spinal anaesthesia adversely affects both the mother and fetus. Although several studies have used pulse oximetry-derived indices, such as pulse perfusion index (PI) and Pleth variability index (PVI), to predict hypotension after spinal anaesthesia, the predictive ability of the PI and PVI remain controversial.

Methods and analysis We prepared this protocol following the Preferred Reporting Items for Systematic Reviews and Meta- Analyses Protocols guidelines. We will conduct searches of MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, European Union Clinical Trials Register (EU-CTR), WHO International Clinical Trials Registry Platform (ICTRP) and University Hospital Medical Information Network Clinical Trials Registry (UMIN) from inception until 5 October 2022. We will include retrospective and prospective observational studies and randomised controlled trials that evaluated the predictive ability of PI and PVI for hypotension after spinal anaesthesia for caesarean section, published in any language. We will exclude case reports, case series and animal studies. Two authors will independently scan and select eligible studies and perform data extraction and assessment of risk of bias. We will estimate predictive ability of PI and PVI as indices of hypotension after spinal anaesthesia for caesarean section using the Rietsma-type bivariate random-effects synthesis model and the hierarchical summary receiver operating characteristic curve. We will assess the quality of evidence using the Grading of Recommendation Assessment, Development and Evaluation approach.

Ethics and dissemination Ethics approval is not required as the systematic review will use existing published data. The results will be submitted for publication in a peer-reviewed journal.

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INTRODUCTION

Rationale In general, caesarean sections are performed under spinal anaesthesia, which is considered to have a lower risk of complications than general anaesthesia.1 However, hypotension frequently occurs during spinal anaesthesia as a result of the sympathetic block, with an estimated incidence of up to 70%.2 Hypotension causes nausea and vomiting in the mother and decreased Apgar score and acidosis in the fetus. Thus, hypotension adversely affects both the mother and fetus,3 and longer duration of hypotension may affect the neurologic prognosis of the fetus.3 Therefore, predicting which patients are prone to hypotension may lead to the implementation of preventive measures, such as the use of vasoactive drugs and increased monitoring with frequent blood pressure measurements, for patients at high risk of hypotension, thereby improving clinical outcomes.

The perfusion index (PI) and Pleth variability index (PVI) are derived from pulse oximetry. PI is a measure of peripheral vascular tone and PVI is a measure of infusion responsiveness that reflects respiratory variability in PI.4 5 Although several studies have used these pulse oximetry-derived indices to predict hypotension after spinal anaesthesia, the predictive ability of these indices remain controversial.4-8

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols statement was followed in preparing the protocol, and the appropriate systematic review and meta-analytic techniques will be applied.
⇒ There may be heterogeneity between the relevant studies; the primary studies may use different definitions of hypotension, infusion load, status and anaesthesia techniques.
⇒ Other potential limitations include the presence of missing unpublished data.
**Objectives**
The aim of this study is to investigate the predictive ability of PI and PVI for hypotension after spinal anaesthesia for caesarean section.

**METHODS AND ANALYSIS**
This protocol follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols and Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 2.

**Eligibility criteria**
**Study designs**
We will consider retrospective and prospective observational studies and randomised controlled trials published in any language. We will exclude case reports, case series and animal studies.

**Patients**
We will include studies examining patients who underwent caesarean section under spinal anaesthesia.

**Index test**
The index tests will be to determine PI and PVI. PI and PVI are indices derived from pulse oximetry. PI is an index of peripheral vascular tone calculated by detecting the pulsatile and non-pulsatile components of infrared light of arterial blood. PI, the ratio of the pulsatile infrared signal to the non-pulsatile infrared signal, is expressed as a percentage. PVI is an index of circulating blood volume based on respiratory variations in PI. PVI is a measure of the dynamic change in PI throughout the respiratory cycle and is calculated using the following formula: 

$$\text{PVI} = \left( \frac{\text{maximum perfusion index} - \text{minimum perfusion index}}{\text{maximum perfusion index}} \right) \times 100.$$  

**Target condition**
The target condition will be hypotension after the induction of spinal anaesthesia. The definition of hypotension in each primary study will be used as the definition of hypotension.

**Information sources and search strategy**
We will conduct a search of MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Clinicaltrials.gov, European Union Clinical Trials Register (EU-CTR), WHO International Clinical Trials Registry Platform (ICTRP) and University Hospital Medical Information Network Clinical Trials Registry (UMIN). We plan to search these databases from their inception until 8 October 2022. The search strategy for PubMed is shown in table 1. Search strategies for all other databases, registries and websites are shown in the online supplemental file 1.

**Table 1**

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**Study records**
**Data management and selection process**
The title and abstracts of papers identified by the search strategies described above will be screened by two authors (YK and EN) independently. We will use Endnote to remove duplicates, and export the remaining titles to Rayyan. If study eligibility cannot be determined from the title or abstract, the full paper will be retrieved. Disagreements about study eligibility will be resolved by discussion.

**Data collection**
Two authors (YK and EN) will extract data independently and in duplicate from each eligible study. Disagreements about extraction will be resolved by discussion. We will contact study authors to resolve uncertainties.

**Data items**
A data collection sheet has been created and included data are (1) author information, (2) year of publication, (3) study design, (4) eligibility criteria, (5) exclusion criteria, (6) type of index test (PI or PVI), (7) cut-off value of index test, (8) definition of hypotension, (9) type of reference standard, (10) total number of patients, total number of (11) true positives, (12) false positives, (13) false negatives and (14) true negatives, for each test, (15) type and dose of anaesthetic drug used, (16) type of anaesthesia (spinal anaesthesia or combined spinal epidural anaesthesia), (17) prophylactic administration of vasopressors, and (18) prophylactic fluid loading.

**Outcomes and prioritisation**
**Primary outcome**
The primary outcome will be the ability of PI and PVI to predict hypotension after spinal anaesthesia for caesarean section. We will report summary diagnostic measures.
such as sensitivity, specificity and summary receiver operating characteristic (SROC) curve (see ‘Data Synthesis’ section).

**Risk of bias in individual studies**

We will assess risk of bias using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool. QUADAS-2 has four domains: patient selection, index test, reference standard, and flow and timing.

Two reviewers independently assessed the risk of bias of the included studies. Disagreements will be resolved by discussion.

**Data synthesis**

First, we will summarise the outcome measures for individual studies, based on the numbers of true positives, false positives, false negatives and true negatives. We will calculate sensitivities and specificities, with corresponding 95% CIs. We will present coupled forest plots to depict sensitivities and specificities for PI and PVI, and generate scatter plots for the pairs of sensitivities and specificities to undertake initial exploratory evaluations and assess heterogeneities.

If the articles show only an association between PI/PVI and hypotension, we will request the source data from the authors. If the authors provide the data, we will count the number of true positives, true negatives, false positives and false negatives according to a predetermined threshold value and include them in the meta-analysis. If the authors have a predefined threshold value, we will adopt it. If there is no assumed threshold value, we will use our predefined threshold value of 3.5 for PI and 20 for PVI.

Second, we will perform synthesis analyses using Reitsma’s bivariate random-effects model, for study-specific sensitivities and specificities to address possible heterogeneities across the studies. Based on the results of synthesis, we will estimate the summary sensitivities and specificities and their heterogeneity variances ($\tau^2$). In addition, we will create SROC curves, based on the estimates of the bivariate random-effects model. We will present the areas under the curves (AUCs) of the SROC curves as summary measures of predictive accuracy measures. For statistical inferences, we will use the standard restricted maximum likelihood estimation for the Reitsma’s model, and we will use the bootstrap method to calculate the 95% CIs of the AUCs of the SROC curves. To assess potential publication biases, we will perform the generalised Egger test for multivariate meta-analysis.

If different thresholds are adopted among the eligible studies, subgroup analyses will be considered according to the prespecified clinically relevant thresholds, including ≤2, 2–5 and >5 for PI and ≤15%, 15–25% and >25% for PVI. In addition, to evaluate possible heterogeneity, we will perform subgroup analyses based on the following variables: definition of hypotension, type of reference standard, type and dose of anaesthetic drug used, type of anaesthesia, presence or absence of prophylactic administration of vasopressors or fluid loading.

We also plan to perform a sensitivity analysis after excluding studies with a high risk of bias.

Statistical analyses will be performed using R software (R Development Core Team, Vienna, Austria) and RStudio (RStudio, Boston, MA, USA).

**Confidence of cumulative evidence**

We will assess the certainty of evidence of outcomes using the Grading of Recommendations Assessment, Development and Evaluation approach. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. In cases where a published study protocol or clinical trial registry is found, the outcomes described in the study protocol or registry will be compared with those reported in the article to assess whether there is selective reporting of outcomes (outcome reporting bias). Quality of evidence will be judged as high, moderate, low or very low.

**Patient and public involvement**

None.

**ETHICS AND DISSEMINATION**

Ethics approval is not required as the systematic review will use existing published data. The results will be submitted for publication in a peer-reviewed journal.

Any significant changes to this protocol will be noted with a description of the change, the corresponding rationale and the date of the amendment, when the results are reported.

**DISCUSSION**

The systematic review will summarise evidence for the predictive ability of PI and PVI for hypotension after spinal anaesthesia in patients undergoing a caesarean section.

Hypotension during spinal anaesthesia is caused by decrease in vascular resistance due to sympathetic blockade and decrease in cardiac output due to vasodilation. Baseline circulating blood volume and vascular tone may influence the tendency for hypotension. In other words, in patients with low vascular tone at baseline, sympathetic blockade caused by spinal anaesthesia may further increase blood pooling in the lower part of the body, resulting in hypotension. A systematic review showed peripheral circulatory indices as candidate predictors of hypotension after spinal anaesthesia for a caesarean section, but the results could not be quantitatively synthesised due to the high heterogeneity of the included studies. In the present systematic review, the aim is to focus on PI and PVI and present quantitatively synthesised results.

The present systematic review would provide important data on PI and PVI as predictive indicators of hypotension after spinal anaesthesia in caesarean sections. The clinical
relevance of this study is that the findings would enable the identification of patients that are prone to hypotension using PI and PVI, which may lead to the implementation of preventive measures, such as the use of vasoactive drugs and increased patient monitoring with frequent blood pressure measurements, thereby improving clinical outcomes.

Previous studies have explored the use of prophylactic vasopressors to prevent hypotension during caesarean section under spinal anaesthesia. A systematic review found that phenylephrine significantly reduced the incidence of hypotension compared with placebo. The international consensus statement on managing hypotension during caesarean section under spinal anaesthesia recommends the routine prophylactic use of vasopressors due to the high frequency of hypotension. However, prophylactic vasopressors can cause adverse effects, including reactive hypertension and arrhythmia, even in healthy pregnant women. Thus, the consensus statement advises against their routine use in patients who are relatively less prone to hypotension, such as those with pre-eclampsia or cardiac disease, and suggests evaluating each patient individually.

To reduce the number of patients who receive prophylactic vasopressors and experience adverse effects despite being at low risk for hypotension, it is essential to select patients who are at high risk for hypotension and need prophylactic vasopressors. If our systematic review confirms that preoperative PVI and PI measurements are useful predictors of hypotension, clinicians can make better decisions regarding the prophylactic use of vasopressors. In this scenario, only patients with high PVI and PI values would receive prophylactic vasopressors, reducing unnecessary administration and adverse effects.

This study has several potential limitations. First, there is potential for heterogeneity. There exists clinical and methodological heterogeneity related to the different study designs of the original studies. The definitions of hypotension, infusion load status and anaesthesia methods differ among the primary studies, which may be a source of heterogeneity. Therefore, we plan to perform subgroup analyses for items such as definition of hypotension, type of reference standard, type and dose of anaesthetic drug used, type of anaesthesia and presence or absence of prophylactic administration of vasopressors or fluid loading. Other potential limitations include the presence of missing unpublished data. It is expected that many of the included primary studies will be observational studies, and some studies may not have been preregistered or will not be published due to unfavourable results. Importantly, the results of this systematic review may not be extrapolated to patients undergoing emergency caesarean sections, as many primary studies are expected to include patients undergoing elective caesarean sections.

This systematic review has the potential to uncover research questions that have not yet been explored. For instance, previous studies have demonstrated that pre-eclampsia patients experience less hypotension after spinal anaesthesia than healthy women. This finding could potentially impact the predictive ability of PI/PVI. If no studies have specifically investigated the predictive ability of PI/PVI to detect hypotension in pre-eclampsia patients, this issue may need to be addressed in future research.

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Contributors TM drafted the protocol. YK and EN led the development of the review protocol and drafted the manuscript. TM, YK, EN and SS contributed to the development of the selection criteria, risk of bias assessment strategy and data extraction criteria. TM and SS developed the search strategy. HN provided expertise on statistical analysis. YK, EN, SS, TM and GT read all drafts of the manuscript, provided feedback and approved the final manuscript.

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