Effectiveness of intrathecal dexmedetomidine vs fentanyl as additives to hyperbaric bupivacaine for postoperative analgesia in women undergoing cesarean section: a systematic review protocol

Jorica Boshoff[1] • Maria Fourtounas[1] • Kylesh Pegu[1] • Patricia McInerney[2]

[1]Department of Anesthesiology, Faculty of Health Sciences, The University of the Witwatersrand, Johannesburg, Gauteng, South Africa, and [2]The Wits-JBI Centre for Evidence-Based Practice: A JBI Centre of Excellence, The University of the Witwatersrand, Johannesburg, Gauteng, South Africa

ABSTRACT

Objective: The aim of this review is to compare the effectiveness of intrathecal dexmedetomidine vs fentanyl as additives to hyperbaric bupivacaine in providing postoperative analgesia in patients undergoing cesarean section.

Introduction: Pain following cesarean section remains a challenge, with limited treatment options due to potential undesirable parturient and neonatal side effects. Intrathecal dexmedetomidine has emerged as a favorable alternative to opioid additives to hyperbaric bupivacaine in prolonging postoperative analgesia, but its effectiveness requires further investigation.

Inclusion criteria: The review will evaluate studies of patients who underwent cesarean section under spinal anesthesia where dexmedetomidine and fentanyl were compared as intrathecal additives to hyperbaric bupivacaine for postoperative analgesia. This review will consider randomized controlled trials, non-randomized controlled trials, and prospective cohort studies for inclusion. No limits regarding publication date or language will be applied.

Methods: A preliminary search of PubMed and Cochrane Central Register of Controlled Trials has been conducted to identify relevant index terms and keywords, which will be applied in a second search across PubMed, Cochrane CENTRAL, Scopus, and Embase. Google Scholar, National Library of Medicine (Clinicaltrials.gov), and the World Health Organization International Clinical Trial Registry Platform will be searched to identify unpublished literature. Full-text studies will be subjected to an assessment of methodological quality, and data extraction will be performed independently by 2 reviewers. The results will be presented in both tabular and narrative format and, where possible, pooled into a meta-analysis. A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Summary of Findings will be created to grade the certainty of evidence of the reported outcomes.

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Keywords: analgesia; cesarean section; hyperbaric bupivacaine; intrathecal dexmedetomidine; intrathecal fentanyl

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Introduction

There has been a rising global trend of pregnant patients delivering via cesarean section (CS) over the past 3 decades in both developed and developing countries.[1] It is estimated that 15% of births worldwide are via CS.[1] Spinal anesthesia is preferred to general anesthesia by virtue of better clinical parturient and fetal outcomes.[2] Parturient satisfaction, pain control, and quality of recovery is also reported to be improved in patients undergoing CS under spinal anesthesia.[3]

Despite this, pain following CS under spinal anesthesia remains a common and complex problem. Intraoperative and postoperative pain have been quoted as the greatest fears of patients undergoing CS.[4] However, patients are reluctant to be administered

Correspondence: Jorica Boshoff, joriics23@gmail.com
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postoperative analgesics and would tolerate high pain scores rather than expose their newborn to any possible analgesic side effects.[4]

In low- and middle-income countries, pain management is often not prioritized, with poor assessment of pain and failure to administer analgesia as prescribed.[5,6] Suboptimal analgesia post-CS is associated with greater rates of chronic pain, opioid use, delayed functional recovery, impaired maternal-fetal bonding, and postpartum depression.[7] This emphasizes the importance of adequate postoperative analgesia, which must be preoperatively planned to include an individualized multimodal approach that can be commenced in the operating room.[5,8]

When performed with only local anesthetics, spinal anesthesia has a limited duration of action and fails to provide long-lasting postoperative analgesia.[9] A commonly used local anesthetic in the setting of spinal anesthesia for CS is methylparaben-free 0.5% hyperbaric bupivacaine.[10] When administered alone intrathecally, high doses of 12 to 15 mg are required to provide adequate anesthesia, which is complicated by an increased incidence of hypotension and fetal distress.[10] Intrathecal and intravenous additives have been extensively studied to reduce their dose and associated side effects and prolong the analgesic action.

Opioids are commonly employed additives to intrathecal local anesthetics. Numerous side effects of intrathecal opioids have been described, but the 4 most common are pruritus, nausea and vomiting, urinary retention, and respiratory depression, all of which are more frequently observed with the administration of hydrophilic intrathecal opioids, such as morphine.[11] The PROSPECT guidelines for elective cesarean section postoperative pain management in 2021 recommends neuraxial opioids to control postoperative pain post-CS over parenteral administration.[12]

Fentanyl is a phenylpiperidine opioid with a high lipid solubility. In intrathecal doses of 10 to 25 mcg, it has a fast onset of action and a low propensity to cause respiratory depression.[9] Other factors that have made fentanyl a popular intrathecal additive to local anesthetics in patients undergoing CS include its relatively low cost, minimal maternal and virtually no fetal side effects, and decreased dose of intrathecal local anesthetic required.[13] The biggest shortcoming of intrathecal fentanyl is the inability to provide long-lasting analgesia, with effects lasting only 60 to 90 minutes.[10]

In contrast, dexmedetomidine has proved a versatile drug with multiple off-label applications, multiple administration routes, and a favorable side effect profile.[14,15] Dexmedetomidine is not currently approved by the US Food and Drug Administration for neuraxial administration, but trials from Asian countries have shown it to be a favorable alternative to opioids in prolonging postoperative analgesia for CS when added to intrathecal hyperbaric bupivacaine.[16,17] It is a highly selective α_2-adrenoreceptor agonist with a high lipophilicity. As a result of the latter, it shortens the duration of onset and prolongs the duration of analgesia provided by regional and neuraxial anesthesia, regardless of whether administered via intrathecal or intravenous routes.[18]

Dexmedetomidine-related side effects during intravenous administration are mostly cardiovascular in nature, notably hypotension and bradycardia. A systematic review and meta-analysis by Wang *et al.*[19] evaluating the effect of 5 mcg intrathecal dexmedetomidine compared with normal saline as an additive to intrathecal bupivacaine in CS concluded that there was no increase in the incidence of hypotension, bradycardia, or nausea and vomiting. The incidence of hypotension and bradycardia has been reported as statistically comparable between doses of ≤ 10 mcg when used as an intrathecal local anesthetic additive, with ephedrine and atropine suggested as treatment, respectively.[20]

Wang *et al.*[19] also found that intrathecal dexmedetomidine reduced the incidence of intraoperative parturient shivering compared with placebo. An attractive feature of dexmedetomidine is its virtual absence of clinically significant effects on respiratory drive. Intravenous dosing of 1 to 2 mcg/kg has been reported to result in mild hypercarbia, mainly via a decrease in tidal volume, but despite this, dexmedetomidine has been used without major respiratory effects in patients undergoing bariatric surgery.[21] Another beneficial effect of intrathecal dexmedetomidine is a reduction in the surgical stress response, as demonstrated by lower postoperative levels of parturient cortisol, interleukin 6, and C-reactive protein when compared with placebo.[22] Dexmedetomidine has also received much attention as a neuroprotective agent by virtue of its antioxidant and anti-inflammatory properties, inhibition of neuronal cell apoptosis, and promotion of neurogenesis.[23]

A 2017 systematic review and meta-analysis by Zhang *et al.*[24] evaluating fetal responses after preoperative parturient dexmedetomidine administration via intravenous, intrathecal, and epidural routes found no adverse effects when compared with placebo with regard to fetal pH, partial pressure of arterial carbon dioxide and oxygen, base excess, and Apgar scores at 1 and 5 minutes. Safe neuraxial use of dexmedetomidine in normal vaginal delivery and CS has been described in patients with complex comorbidities.[25]

A preliminary search of PROSPERO, PubMed, the Cochrane Database of Systematic Reviews, and *JBI Evidence Synthesis* was conducted, and no current or in-progress systematic reviews on the topic were identified. The objective of this review is to compare the effectiveness of intrathecal dexmedetomidine with intrathecal fentanyl as additives to hyperbaric bupivacaine in the management of postoperative pain in patients undergoing CS.

The review aims to contribute to simple and feasible management of postoperative pain by utilizing practices already well established. Neuraxial anesthesia is the preferred modality of anesthesia to facilitate CS.[2] The postpartum period presents immense adjustments for any birthing parent, and early effective pain management is of the utmost importance.

Review question

What is the effectiveness of intrathecal dexmedetomidine vs fentanyl as additives to hyperbaric bupivacaine for providing postoperative analgesia in patients undergoing CS?

Inclusion criteria

Participants

This review will consider studies that include patients who underwent CS under spinal anesthesia. All pregnant patients without contraindications to, and giving consent for, spinal anesthesia will be considered, with no limitation on age or number of fetuses in the pregnancy.

Interventions

This review will consider studies that utilize the single administration of only intrathecal dexmedetomidine 2 to 15 mcg as an additive to any dose of intrathecal hyperbaric bupivacaine administered in the operating room for the purpose of CS.

Studies where additional agents or interventions capable of profound analgesia, such as those contained in Steps 3 and 4 of the updated World Health Organization (WHO) Pain Ladder,[26] were administered prior to the patient's first request for analgesia will be excluded. Agents and interventions include strong opioids, epidural administrations, single-dose or continuous infusion fascial plane blocks, or patient-controlled analgesia infusions. Studies where simple analgesic agents and weak opioids, such as those contained in Steps 1 and 2 of the WHO Pain Ladder,[26] were administered prior to the patient's first request for analgesia will be considered for inclusion.

Comparator

This review will consider studies that compare the intervention to the single administration of only intrathecal fentanyl 10 to 25 mcg as an additive to any dose of intrathecal hyperbaric bupivacaine administered in the operating room for the purpose of CS.

Outcomes

This review will consider studies that evaluate the following outcomes: postoperative pain at any time in the postoperative period quantified by the patient using pain rating scales, such as a visual analogue scale or a numerical pain rating scale; duration of analgesia measured by time to first patient request for analgesia, which can be administered via any modality; duration of motor block measured by time to full motor recovery, measured using the modified Bromage score; and the incidence of adverse events, such as nausea and vomiting, hypotension, bradycardia, or shivering.

Types of studies

This review will consider both experimental and quasi-experimental study designs, including randomized controlled trials and non-randomized controlled trials. In addition, analytical observational studies, including prospective cohort studies, will be considered for inclusion. No limits regarding publication date or language will be applied.

Methods

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of effectiveness.[27] The protocol will be reported according to the Preferred Reporting Items

for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[28] The protocol is registered with PROSPERO (CRD42022364815).

Search strategy

The search strategy will aim to locate both published and unpublished studies and will employ a 3-phase search strategy. An initial limited search of PubMed and the Cochrane Central Register of Controlled Trials was conducted to identify studies on the topic. The text words contained in the titles and abstracts of relevant studies, and the index terms used to describe the studies were used to develop a full search strategy for the Cochrane Central Register of Controlled Trials via EBSCOhost (see Appendix I). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference lists of all studies selected for critical appraisal will be screened for additional studies. The databases to be searched are PubMed (EBSCOhost), Cochrane Central Register of Controlled Trials (EBSCOhost), Scopus, and Embase (Ovid). Google Scholar (first 20 pages), National Library of Medicine (Clinicaltrials.gov), and the WHO International Clinical Trial Registry Platform will be examined for unpublished studies.

Study selection

Following the search, all identified citations will be collated and uploaded into Zotero (Corporation for Digital Scholarship and Roy Rosenzweig Center for History and New Media, VA, USA) and duplicates removed. Titles and abstracts will then be screened by 2 independent reviewers for assessment against the inclusion criteria for the review. Where studies in languages other than English are identified, the paper will be assessed for applicability using Google Translate and, if applicable, a more accurate translation will be sought from the JBI Collaboration Centers. As a result of the small number of studies retrieved during the preliminary searches, piloting of the various stages of the systematic review will not be undertaken. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[29] The full text of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a PRISMA flow diagram.[30]

Assessment of methodological quality

Eligible studies will be critically appraised by 2 independent reviewers at the study level for methodological quality using the JBI critical appraisal checklists for quantitative studies.[27] Methodological quality of the appraised studies will be reported as low (0–39% "yes" responses), moderate (40–79% "yes" responses), or high (80–100% "yes" responses). Authors of papers will be contacted to request missing or additional data for clarification for a maximum of 2 attempts, where required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of the critical appraisal will be reported in a table with accompanying narrative. All studies, regardless of their methodological quality, will undergo data extraction and synthesis. Due consideration will be given to the assessed methodological quality of the studies during synthesis of the evidence to indicate the effect of moderate- and low-quality studies on the overall results, if present.

Data extraction

Data will be extracted from studies included in the review by 2 independent reviewers using the standardized JBI data extraction tool in JBI SUMARI.[29] The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review question. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data for a maximum of 2 attempts, where required.

Data synthesis

Studies will, where possible, be pooled with statistical meta-analysis using JBI SUMARI.[29] Effect sizes will be expressed as either odds ratios (for

dichotomous data) or weighted (or standardized) final post-intervention mean differences (for continuous data) and their 95% CI will be calculated for analysis. Heterogeneity will be assessed statistically using the standard χ^2 and I^2 tests. Statistical analyses will be performed using the random-effects model in the presence of moderate or high heterogeneity ($I^2 > 50\%$); in their absence, the fixed-effects model will be applied.[31] Subgroup analyses will be conducted where there are sufficient data to investigate study design, participant characteristics, dosages of intrathecally administered medications, duration of surgery, administration of postoperative analgesia, and time of pain score assessment. Sensitivity analyses with a random-effects model will be conducted to test decisions made regarding inclusion of large trials and the effect of studies with low and moderate methodological quality. Where statistical pooling is not possible, the findings will be presented narratively, including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry, such as the Egger test,[32] will be performed where appropriate. In the event that statistical pooling is not feasible, findings will be presented narratively, including graphical representation of the data, where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed.[33] A Summary of Findings will be created using GRADEpro software (McMaster University, ON, Canada). The Summary of Findings will present the following information where appropriate: absolute risks for the treatment and control; estimates of relative risk; and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. All outcomes will be included in the Summary of Findings.

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Declarations

JB is a registrar in the Department of Anesthesiology of the University of the Witwatersrand, Johannesburg, and frequently administers spinal anesthesia to patients presenting for emergency and elective CS at the government hospitals affiliated with the University of the Witwatersrand. MF and KP are both South African board–qualified anesthesiologists currently practicing in the private health care sector in South Africa.

Author contributions

The manuscript was written by JB and reviewed by MF, KP, and PM. PM provided advice and guidance, MF provided access to Embase, and KP assisted with document formatting.

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Appendix I: Search strategy

Cochrane Central Register of Controlled Trials (EBSCOhost)

Search conducted: August 28, 2023

Search	Query	Records retrieved
#1	([mh "cesarean section"] OR cesarean section):ti,ab,kw (Word variations have been searched)	14,469
#2	([mh "bupivacaine"] OR bupivacaine):ti,ab,kw (Word variations have been searched)	15,858
#3	([mh "dexmedetomidine"] OR dexmedetomidine):ti,ab,kw (Word variations have been searched)	8298
#4	([mh "fentanyl"] OR fentanyl):ti,ab,kw (Word variations have been searched)	18,748
#5	#1 AND #2 AND #3 AND #4	29
No filters applied		