Effectiveness of intrathecal dexmedetomidine versus fentanyl as additives to hyperbaric bupivacaine on postoperative analgesia in patients undergoing Cesarean section: a systematic review and meta-analysis

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ABSTRACT

Objective: This review compared the effectiveness of intrathecal dexmedetomidine with fentanyl as additives to hyperbaric bupivacaine for providing postoperative analgesia after Cesarean section.

Introduction: There are limited treatment options for pain following Cesarean section due to potential parturient and neonatal side effects. Intrathecal dexmedetomidine has emerged as an alternative to intrathecal opioids for prolonging postoperative analgesia, but its effectiveness requires further investigation.

Eligibility criteria: The review evaluated studies of patients who underwent Cesarean section under spinal anesthesia where dexmedetomidine and fentanyl were compared as intrathecal additives to hyperbaric bupivacaine. The outcomes were postoperative pain scores in the first 24 hours, duration of analgesia, duration of motor block, and the incidence of side effects. Randomized controlled trials, non-randomized controlled trials, and prospective cohort studies were considered.

Methods: PubMed, Cochrane Central Register of Controlled Trials, Scopus, and Embase were searched in September 2023 and May 2024. ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and Google Scholar were searched for gray literature. Study selection, critical appraisal, data extraction, and data synthesis were conducted using the JBI methodology for systematic reviews of effectiveness. Assessment of the certainty in findings was conducted using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results: Fifteen studies (13 RCTs and 2 non-randomized, prospective cohort studies) with 1098 participants were included. The overall risk of bias was moderate. There was low to moderate certainty that dexmedetomidine results in lower pain scores up to 6 hours postoperatively, with only the difference at 4 hours greater than the minimum clinical important difference of 1 point on a numeric pain rating scale (2 RCTs, 100 participants; mean difference [MD] 1.26 points lower, 95% CI 1.78 to 0.74). There was low certainty that dexmedetomidine prolongs the duration of analgesia (8 RCTs, 578 participants; MD 93.3 minutes, 95% CI 62.40 to 124.19). There was very low certainty that dexmedetomidine prolongs the duration of motor block (8 RCTs, 502 participants; MD 29.68 minutes, 95% CI 0.96 to 58.40). There was low certainty that dexmedetomidine increases the risk of hypotension (10 RCTs, 688 participants; absolute difference of 2% increase in risk, 95% CI 6% decrease to 11% increase) and bradycardia (8 RCTs, 558 participants; absolute difference of 2% increase in risk, 95% CI 2% decrease to 8% increase). There was moderate certainty that dexmedetomidine decreases the risk of nausea and vomiting (8 RCTs, 558 participants; absolute difference of 7% decrease in risk, 95% CI 11% to 0% decrease); pruritus (7 RCTs, 442 participants; absolute difference of 11% decrease in risk, 95% CI 11% to 9% decrease); and shivering (5 RCTs, 390 participants; absolute difference of 8% decrease in risk, 95% CI 9% decrease to 3% decrease).

Conclusions: Dexmedetomidine probably results in a meaningfully lower pain score, limited to the fourth hour postoperatively, and may result in a longer duration of analgesia. Dexmedetomidine probably results in lower incidence of nausea and vomiting, pruritus, and shivering. Dexmedetomidine may increase the incidence of hypotension and bradycardia. It is uncertain whether dexmedetomidine results in a longer duration of motor block.

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The authors declare no conflict of interest.

DOI: 10.11124/JBIES-24-00418

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

JBI Evid Synth 2025; 23(12):2379–2418.

Summary of Findings

Dexmedetomdine compared with fentanyl in spinal anesthesia as an additive to hyperbaric bupivacaine for women undergoing Cesarean section

Bibliography: Boshoff J, Fourtounas M, Pegu K, McInerney P. Effectiveness of intrathecal dexmedetomidine vs fentanyl as additives to hyperbaric bupivacaine for postoperative analgesia in women undergoing Cesarean section: a systematic review and meta-analysis. JBI Evid Synth. 2025;23(12):2379-2418.

Interactive Summary of Findings: https://gdt.gradepro.org/presentations/#/isof/isof_994d3baa-6707-4d72-82ed-11c4021f5718-1760594175965

Outcomes	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pain score at 1 hour post CS assessed with NPRS from 0 to 10 points	*Fentanyl:* The mean pain score at 1 hour post-CS was **1.71** points *Dexmedetomidine:* MD **0.24 points lower** (0.60 points lower to 0.12 points higher)	—	170 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomidine probably results in a lower but not meaningful reduction in NPRS at 1 hour post CS.
Pain score at 4 hours post CS assessed with: NPRS from 0 to 10 points	*Fentanyl:* The mean pain score at 4 hours post-CS was **4.86** points *Dexmedetomidine:* MD **1.26 points lower** (1.78 points lower to 0.74 points lower)	—	100 (2 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomdine probably results in a meaningful reduction in NPRS at 4 hours post CS.
Pain score at 6 hours post CS assessed with NPRS from 0 to 10 points	*Fentanyl:* The mean pain score at 6 hours post-CS was **7.17** points *Dexmedetomidine:* MD **0.27 points lower** (0.71 points lower to 0.17 points higher)	—	150 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	Dexmedetomidine probably results in a lower but not meaningful reduction in NPRS at 6 hours post CS.
Duration of analgesia assessed with time to first request for additional analgesia (in minutes)	*Fentanyl:* The mean duration of analgesia was **250.42** minutes *Dexmedetomidine:* MD **93.3 minutes more** (62.40 to 124.19 minutes more)	—	578 (8 RCTs)	⊕⊕◯◯ Low[a,c]	Dexmedetomidine may result in a longer duration of analgesia.
Duration of motor block assessed with time to Bromage score of 0 (in minutes)	*Fentanyl:* The mean duration of motor block was **187** minutes *Dexmedetomidine:* MD **29.68 minutes more** (0.96 to 58.40 minutes more)	—	502 (8 RCTs)	⊕◯◯◯ Very low[a,c,d]	The evidence is uncertain whether dexmedetomidine results in a longer duration of motor block.
Hypotension assessed with number of patients who developed intraoperative hypotension	*Fentanyl:* 29 per 100 *Dexmedetomidine:* **31 per 100** (23 to 40 per 100)	**OR 1.09** (0.73 to 1.64)	688 (10 RCTs)	⊕⊕◯◯ Low[a,b]	Dexmedetomidine may result in an increase in the incidence of hypotension.
Bradycardia assessed with number of patients who developed intraoperative bradycardia	*Fentanyl:* 7 per 100 *Dexmedetomidine:* **9 per 100** (5 to 15 per 100)	**OR 1.22** (0.66 to 2.27)	558 (8 RCTs)	⊕⊕◯◯ Low[a,b]	Dexmedetomidine may result in an increase in the incidence of bradycardia.
Nausea and vomiting assessed with number of patients who developed intraoperative nausea and vomiting	*Fentanyl:* 18 per 100 *Dexmedetomidine:* **11 per 100** (7 to 17 per 100)	**OR 0.57** (0.34 to 0.97)	558 (8 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomidine probably results in a decrease in the incidence of nausea and vomiting.

(*Continued*)

Outcomes	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pruritus assessed with number of patients who developed intraoperative pruritus	*Fentanyl:* 11 per 100 *Dexmedetomidine:* **1 per 100 (0 to 3)**	**OR 0.06** (0.02 to 0.22)	442 (7 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomidine probably results in a decrease in the incidence of pruritus.
Shivering assessed with number of patients who developed intraoperative shivering	*Fentanyl:* 11 per 100 *Dexmedetomidine:* **3 per 100** (1 to 7)	**OR 0.28** (0.12 to 0.65)	390 (5 RCTs)	⊕⊕⊕◯ Moderate[a]	Dexmedetomidine probably results in a decrease in the incidence of shivering.

CS, Cesarean section; MD, mean difference; NPRS, numeric pain rating scale; OR, odds ratio; RCT, randomized controlled trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a) Downgraded for risk of bias: Unclear randomization and/or allocation procedure; treatment groups were not similar at baseline or it was unclear; unclear if there was blinding of participants and/or those delivering treatment and/or outcome assessors; unclear if follow-up was complete.
b) Downgraded for imprecision: Optimal information size was not met.
c) Downgraded for inconsistency: Wide variance in point estimates and considerable I^2 value all likely to lower confidence in estimate of effect.
d) Downgraded for indirectness: Bromage score was used as a surrogate measurement since time to full motor block resolution was determined as time to reach a Bromage score of 3.

Introduction

Rates of Cesarean section (CS) have increased over the past decades to the extent that it is one of the most commonly performed major abdominal surgeries.[1,2] CS performed under spinal anesthesia results in better parturient and fetal outcomes compared with general anesthesia, with reports showing improved parturient quality of recovery as evidenced by greater satisfaction with postoperative pain control, earlier mobilization, and a return to activities of daily living.[3,4] Pain during the intraoperative and postoperative periods has been cited among the greatest fears of parturients undergoing CS.[5] Suboptimal pain control following CS has immediate negative effects on parturients and newborns, including increased postoperative opioid requirements, impaired maternal–fetal bonding, delayed recovery, and higher risk of developing postpartum depression.[6] Late-onset effects of poor postoperative pain control contribute to the burden of chronic disease through higher rates of chronic pain.[6]

A perpetuating factor especially relevant in low- and middle-income countries is the low priority often assigned to postoperative pain management, whether as a result of ignorance regarding pain assessment or understaffing, with failure to administer analgesia as prescribed.[7,8] Postoperative CS analgesia must be planned in the preoperative period and must involve multimodal strategies.[7,9] Postoperative analgesia can be provided based on a stepwise approach, as demonstrated by the World Health Organization (WHO) Pain Ladder.[10]

An important component of pain management that can be commenced in the operating room is the intrathecal administration of analgesic agents not only to provide surgical anesthesia to facilitate CS but also to provide analgesia extending well into the postoperative period.[11] An equally important but conflicting concern of parturients is that of exposing their newborn to potential side effects of systemically administered analgesic agents.[5] Intrathecal administration of analgesic agents results in negligible placental and breast milk transfer, and reduces requirements for systemic opioids.[12,13] A combination of fentanyl, a lipophilic opioid dosed at ≤0.25 mcg/kg, and methylparaben-free 0.5% hyperbaric bupivacaine at a conventional dose of 10 mg for spinal anesthesia in CS has been established as favorable. When compared to bupivacaine alone, a fentanyl-bupivacaine combination prolongs the time to onset of postoperative pain, does not significantly increase the duration of motor block, and reduces the dose of bupivacaine required, subsequently reducing the incidence of side effects

associated with conventional and high-dose bupivacaine (eg, hypotension, nausea, vomiting, shivering).[12,13] Intrathecal fentanyl also has a low risk of causing respiratory depression.[14] The main shortfall of the hyperbaric bupivacaine-fentanyl combination is an inability to provide analgesia extending
into the postoperative period and a notable increase in the incidence of pruritus.[14,15]

Dexmedetomidine, a lipophilic selective α_2 agonist, is not currently approved by the US Food and Drug Administration for neuraxial administration, and its application in obstetric anesthesia is not commonplace. However, it has been a subject of interest, prompting research that explores its role in obstetric anesthesia. Its use via the intravenous and intrathecal routes for labor analgesia and anesthesia for CS has been described in patients with complex comorbidities.[16] A systematic review by Shen *et al.*[17] investigated the effect of 2.5 to 7.5 mcg intrathecal dexmedetomidine added to bupivacaine on the incidence of parturient side effects and on neonatal Apgar scores compared with normal saline placebo. No difference in Apgar scores was demonstrated, and there was no increase in the incidence of hypotension, bradycardia, or nausea and vomiting. A decrease in the incidence of shivering was noted in the intrathecal dexmedetomidine group. These findings in the obstetric population are consistent with results from systematic reviews by Wang *et al.*[18] and Zhang *et al.*[19] 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.[20]

Adequate postoperative analgesia, early mobilization, prevention of nausea and vomiting, and perioperative glucose control (in part via attenuation of the surgical stress response) are some of the elements recommended to enable enhanced recovery after CS (ERAC).[11] Current ERAC guidelines recommend the administration of long-acting intrathecal opioids such as morphine to provide postoperative analgesia. Intrathecal opioid use, however, has a risk of side effects that impede some ERAC components, such as nausea, vomiting, pruritus,[11] and concern for delayed onset of postoperative respiratory depression.[21]

The evidence suggests that intrathecal dexmedetomidine potentially has a role to play in ERAC. The aim of this systematic review was to compare the analgesia provided by the combination of intrathecal dexmedetomidine and hyperbaric bupivacaine vs intrathecal fentanyl and hyperbaric bupivacaine for parturients undergoing CS. An additional aim was to compare the side effect profiles of these combinations to further establish whether dexmedetomidine is a suitable or potentially superior alternative to fentanyl.

A preliminary search of PROSPERO, MEDLINE, 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.

Review question

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

Eligibility criteria

Participants

This review considered studies of patients who underwent CS under spinal anesthesia. All pregnant patients giving consent for spinal anesthesia, and who did not have contraindications, were considered, with no limitation on patient age or number of fetuses in the pregnancy.

Intervention

This review considered studies that used the single administration of intrathecal dexmedetomidine alone in the dose range of 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 were excluded if additional agents or interventions capable of profound analgesia, such as those in steps 3 and 4 of the updated WHO Pain Ladder,[10] were administered prior to the patient's first request for analgesia. The following agents and interventions were excluded: strong opioids, epidural administrations, single-dose or continuous infusion fascial plane blocks, wound infusion catheters, and patient-controlled analgesia infusions. Studies where simple analgesic agents and weak opioids, such as those in steps 1 and 2 of the WHO Pain Ladder,[10] were administered prior to the patient's first request for analgesia were considered for inclusion.

Comparators

This review considered studies that compared the intervention to an active comparator in the form of an alternate intervention. The comparator consisted of the single administration of intrathecal fentanyl alone in the dose range of 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 considered studies that evaluated the following outcomes likely to have occurred in the first 24 hours after CS: postoperative pain at any time in the postoperative period as quantified by the patient using pain rating scales, such as a visual analogue scale (VAS) or a numeric pain rating scale (NPRS); duration of analgesia measured by time from intrathecal administration to first patient request for analgesia, which could be administered via any modality; duration of motor block measured by time to full motor recovery, measured using the basic Bromage score; and the incidence of side effects, such as nausea and vomiting, hypotension, bradycardia, shivering, and pruritus.

Types of studies

This review considered both randomized controlled trials (RCTs) and non-RCTs. Analytical observational studies, such as prospective cohort studies, were also considered. Retrospective observational study designs were not deemed suitable to assess the review question due to many of the outcomes of interest occurring within a short period of time, the rapid turnover of obstetric patients with limited time to record outcomes, and the intervention of interest being off label and not current standard practice.

Methods

This systematic review was conducted in accordance with JBI methodology for systematic reviews of effectiveness.[22] An a priori protocol[23] was developed and registered with PROSPERO (CRD42022364815).

Search strategy

A 3-step search strategy was used in this review to find both published and unpublished studies. First, an initial limited search of PubMed (EBSCOhost) and Cochrane Central Register of Controlled Trials (CENTRAL; EBSCOhost) was undertaken, followed by analysis of the text words contained in the titles and abstracts, and the index terms used to describe each study. The search strategy, including all identified keywords and index terms, was adapted for individual searches in PubMed (EBSCOhost), Cochrane CENTRAL (EBSCOhost), Embase (Ovid), and Scopus (EBSCOhost). A second search was undertaken in September 2023 and again in May 2024. The full search strategies were reviewed by all authors and are provided in Appendix I. Google Scholar (first 20 pages), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (WHO ICTRP) were examined for gray literature, unpublished studies, and studies published in journals not indexed in the searched databases. Finally, the reference lists of studies included in the review were examined for additional studies.

No restrictions on study language were applied, although the search on each database was conducted only in English. All studies found in languages other than English had an English version available. As the use of dexmedetomidine via the intrathecal route is still a novel entity and the initial limited searches of PubMed and Cochrane CENTRAL yielded only a small number of studies, no restriction on publication date was applied, to allow detection of as many studies as possible.

Study selection

Following the search, all identified citations were collated and uploaded into Zotero (Corporation for Digital Scholarship and Roy Rosenzweig Center for History and New Media, VA, USA) and duplicates were removed. As a result of the small number of studies retrieved during the preliminary searches, piloting of the various stages of the systematic review was not undertaken. Following this decision, titles and abstracts were screened by 2 reviewers (JB and MF) independently for assessment against the inclusion criteria for the review. Potentially relevant studies were 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).[24] Full-text studies that did not meet the inclusion criteria were excluded, and reasons for their exclusion are provided in Appendix II. Any disagreements that arose between the reviewers were resolved through discussion.

Assessment of methodological quality

Eligible studies were critically appraised independently by 2 reviewers (JB and MF) at both the study and outcome level for methodological quality using standardized critical appraisal instruments from JBI for experimental and observational studies.[22] In the event of unclear or incomplete reporting, and the authors not responding to requests for more information, the appraisal question was given an *unclear* response. Overall methodological quality of the appraised studies was reported as low (0%–39% "yes" responses), moderate (40%–79% "yes" responses), or high (80%–100% "yes" responses) as specified in the a priori protocol.[23] All studies, regardless of their methodological quality, were included in the review and underwent data extraction and synthesis. Due consideration was given to the assessed methodological quality of the studies during synthesis of the evidence to indicate the effect of moderate-quality and low-quality studies on the overall results. The authors of the papers were contacted to request missing or additional data for clarification up to a maximum of 2 attempts. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer.

Data extraction

Data were extracted from included studies independently by 2 reviewers (JB and MF) using the standardized JBI data extraction tool.[24] Data for the following outcomes were sought for extraction:

- postoperative pain at any time in the postoperative period quantified by the patient using pain rating scales, such as a VAS or an NPRS
- duration of analgesia measured by time from intrathecal administration to first patient request for analgesia, which could be administered via any modality
- duration of motor block measured by time to full motor recovery, indicated with the basic Bromage scale
- incidence of side effects, such as nausea and vomiting, hypotension, bradycardia, shivering, and pruritus.

Specific participant characteristics sought for extraction included the American Society of Anesthesiologists physical status classification, gestational age, urgency of CS, and criteria for exclusion from the studies. Information regarding the doses and total volume of the intrathecally administered intervention and comparator drugs was collected. The drugs and doses used as standard and rescue analgesia were also noted. Additionally, the study country, setting, methodology, and sample size were reported. Any disagreements that arose between the reviewers were resolved through discussion.

Study authors were contacted to request missing data and to clarify unclear information up to maximum of 2 times. Where there was no response, an attempt was made to contact the institution where the study was conducted to request alternative contact details. The authors of 13 studies were contacted, and the authors of 2 studies responded. Where there was no feedback from study authors, studies with contradictory statements were excluded while studies with missing data were noted in the extraction form and not included in data synthesis.

Data synthesis

Studies were, where possible, pooled for statistical meta-analysis using JBI SUMARI.[24] Effect sizes, expressed as either odds ratios for dichotomous data or weighted (or standardized) final post-intervention mean differences (MDs) for continuous data, and their 95% CIs were calculated for analysis. Statistical analyses were performed using the random-effects model in the presence of moderate or high heterogeneity; in their absence, the fixed-effects model was applied.[25] All meta-analyses were visually displayed using forest plots and tables. Subgroup analyses were conducted where there were sufficient data to investigate the different doses of intrathecal hyperbaric bupivacaine, dexmedetomidine, and fentanyl, as well as the drugs employed as standard and rescue analgesia. Sensitivity analyses were performed by sequential removal of single studies at a time where there was moderate to high statistical heterogeneity. Statistical heterogeneity was assessed using the standard χ^2 and I^2 tests, and moderate to high heterogeneity was assumed when I^2>50%. Subgroup analyses were employed to assess clinical and methodological heterogeneity.

Where there were 10 or more studies included in a meta-analysis, a funnel plot was generated using STATA v.18 (Stata Corp LLC, Texas, USA) to investigate for potential publication bias. The regression-based Egger test was performed to investigate for funnel plot asymmetry.

Where meta-analysis was not possible, the findings are presented in narrative format, including tables and figures to aid in data presentation, where appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence was followed,[26] and a Summary of Findings (SoF) as well as an Evidence Profile (EP; Appendix III) were created using GRADEpro GDT v.6 (McMaster University and Evidence Prime, ON, Canada). Study authors were contacted to request missing or additional data for clarification, where required. The optimal information size to comment on precision of dichotomous outcomes when required was calculated using a sample size calculator that can be found at https://www.stat.ubc.ca/~rollin/stats/ssize/b1.html using an α value of 0.05 and a β value of 0.8. Where the minimum clinical important difference (MCID) was known, sample size calculation was performed using a sample size calculator that can be found at https://www.sealedenvelope.com/power/continuous-superiority/ using an α value of 0.05 and a β value of 0.8.

The SoF and EP 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. The outcomes reported in the SoF and EP include pain scores at 1, 4, and 6 hours postoperatively, duration of analgesia, duration of motor block, hypotension, bradycardia, nausea and vomiting, pruritus, and shivering.

Results

Study inclusion

During the literature search, 201 studies were found in the identified databases and registries. Prior to screening, 51 duplicate studies were removed as well as 3 animal studies and 1 retracted meta-analysis.[27] One hundred and forty-six studies underwent title and abstract screening, after which 131 studies were removed. A total of 15 studies were sought for retrieval, with the full text of 4 reports from the searched trial registries unable to be retrieved. The full text of 21 papers were screened, which included 10 studies found in Google Scholar and from citation searching. Six papers were excluded after full-text screening. This included the removal of a study published under the Creative Commons Attribution NonCommercial-ShareAlike 4.0 license.[28] The study[29] shared a lead author, sample size, participant characteristics, outcomes, and results with another study[30] but was published in a different year under a different title with different coauthors. The more recently published study was deemed a duplicate and removed.

The main reason for study exclusion at full-text review was incomplete or unclear study information, with no response from authors after attempts to obtain or clarify information. See Appendix II for details on studies excluded at full-text screening. This consisted of 4 studies that were not clear on whether isobaric or hyperbaric bupivacaine was used. The authors of 2 papers responded to clarify that hyperbaric bupivacaine was used,[31,32] while the authors of the other 2 studies did not respond.[33,34] Two studies were excluded for having ineligible comparators. One study was excluded for having ineligible participant characteristics not evident from the abstract. A total of 15 studies were included for critical appraisal and synthesis in the review. The study selection and inclusion process is presented in Figure 1.[35]

Methodological quality

The overall methodological quality of the 15 included studies was moderate when using the percentage scores previously outlined.[30-32,36-47] Scores ranged from 54% to 92%, with a mean of 75% for the 13 included RCTs (Table 1). For the 2 non-RCTs, the scores were 64% and 80%, with a mean 72% (Table 2). Six RCTs specified the method of randomization (Q1),[30,31,37,38,40,42] which were all by computer-generated allocation sequences. Most of the studies reported double-blinding, with 8 studies stating clearly that participants were blinded to treatment assignment (Q4),[30,32,36-41] 5 stating that those delivering treatment were blinded to treatment assignment (Q5),[30,36,37,39,40] and 6 studies reporting that outcome assessors were blinded to treatment assignment (Q6).[32,36-39,42]

No study reported any differences in their treatment of the study groups other than the intervention of interest (Q7). Follow-up for all RCTs was complete (Q8), although 1 study[39] reported the removal of patients from further pain score assessment after a pain score of >3 was documented and the patient started on standard analgesia, as per hospital protocol. The study did not go on to specify the number of participants

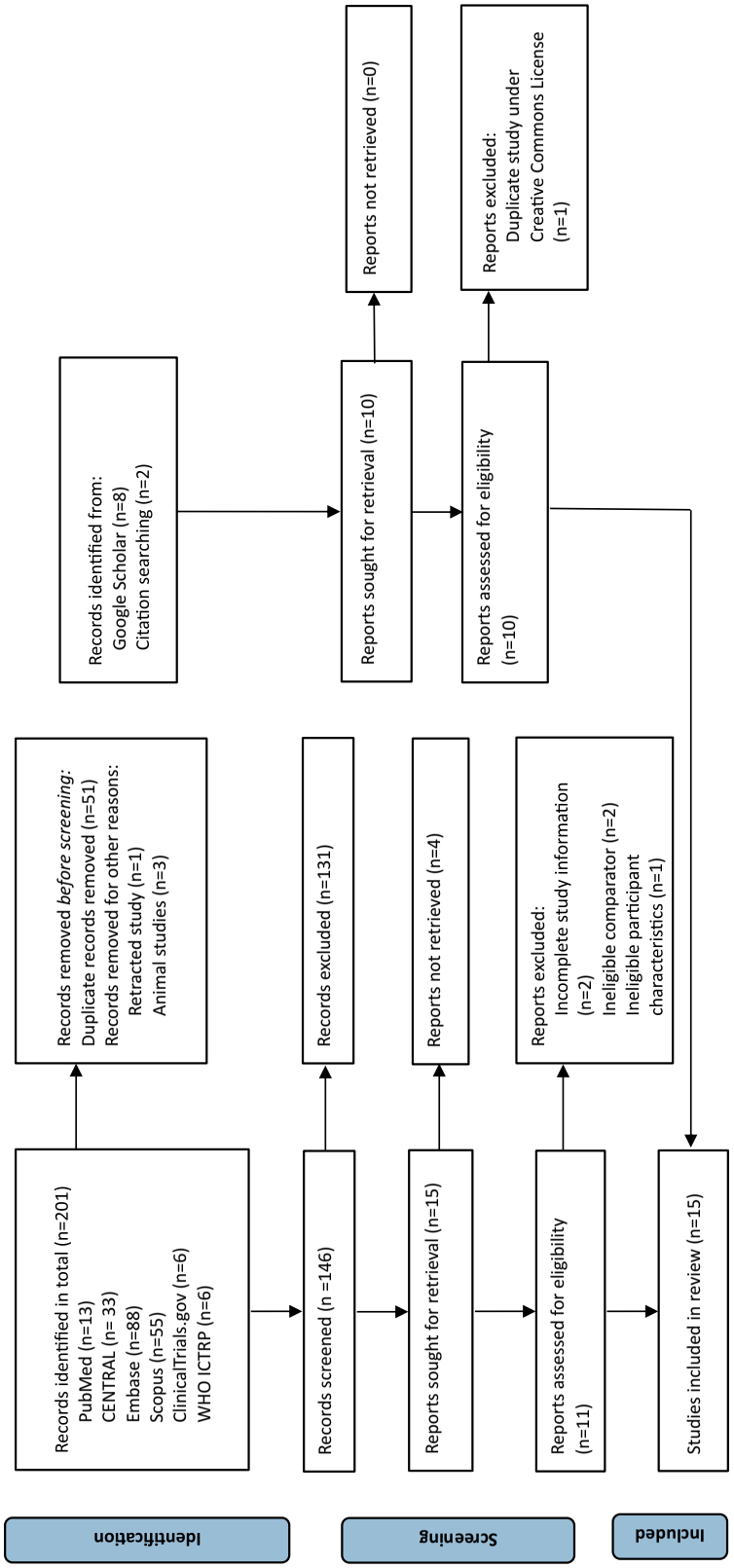


Figure 1: Search results and study selection and inclusion process[35]

Table 1: Critical appraisal of eligible randomized controlled trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% Yes	Methodological quality
Balaji, 2016[44]	U	Y	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	69	Moderate
El-Din *et al.*, 2018[30]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	92	High
Farooq *et al.*, 2022[41]	U	U	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	69	Moderate
Hasan and Manohar, 2019[42]	Y	U	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	77	Moderate
Iqbal *et al.*, 2021[32]	U	U	U	Y	U	Y	Y	Y	Y	Y	Y	U	U	54	Moderate
Khosravi *et al.*, 2020[38]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	92	High
Li, *et al.*, 2015[36]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	85	High
Mahdy and Abdallah 2011[40]	Y	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	85	High
Mishra *et al.*, 2017[43]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	62	Moderate
Rajkumar *et al.*, 2022[31]	Y	U	Y	U	U	U	Y	Y	Y	Y	Y	U	Y	62	Moderate
Rao and Prasad, 2019[45]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	62	Moderate
Sun *et al.*, 2015[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	85	High
Urooj *et al.*, 2022[39]	U	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	77	Moderate
%	46	46	85	62	38	46	100	92	100	100	85	77	92		

Y, yes; N, no; U, unclear
JBI Critical Appraisal Checklist for Randomized Controlled Trials
Q1: Was true randomization used for assignment of participants to treatment groups?
Q2: Was allocation to treatment groups concealed?
Q3: Were treatment groups similar at baseline?
Q4: Were participants blind to treatment assignment?
Q5: Were those delivering treatment blind to treatment assignment?
Q6: Were outcome assessors blind to treatment assignment?
Q7: Were treatment groups treated identically other than the intervention of interest?
Q8: Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?
Q9: Were participants analyzed in the groups to which they were randomized?
Q10: Were outcomes measured in the same way for treatment groups?
Q11: Were outcomes measured in a reliable way?
Q12: Was appropriate statistical analysis used?
Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 2: Critical appraisal of eligible cohort studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	% Yes	Methodological quality
Mohammed *et al.*, 2022[47]	Y	Y	Y	U	U	Y	Y	Y	Y	N/A	Y	80	High
Sheikh *et al.*, 2021[46]	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	64	Moderate
%	100	100	100	0	0	100	100	100	50	0	100		

Y, yes; U, unclear; N/A, not applicable
JBI Critical Appraisal Checklist for Cohort Studies
Q1: Were the 2 groups similar and recruited from the same population?
Q2: Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3: Was the exposure measured in a valid and reliable way?
Q4: Were confounding factors identified?
Q5: Were strategies to deal with confounding factors stated?
Q6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7: Were the outcomes measured in a valid and reliable way?
Q8: Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
Q9: Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
Q10: Were strategies to address incomplete follow-up utilized?
Q11: Was appropriate statistical analysis used?

Table 3: Mean demographic characteristics in intervention and comparator groups of included studies comparing intrathecal dexmedetomidine vs fentanyl for postoperative analgesia in patients undergoing Cesarean section

Parameter (mean)	Dexmedetomidine group	Fentanyl group
Age (years): 14 studies[30-32,36-38,40-47]	27.53	29.12
Weight (kg): 11 studies[30,36-41,43-46]	67.88	69.22
Height (cm): 11 studies[30,36-41,43-46]	159.86	160.33
Intrathecal volume (mL): 11 studies[30,31,36-40,43-47]	2.53	2.56
Hyperbaric bupivacaine dose (mg): 15 studies[30-32,36-47]	10	10
Dexmedetomidine dose (mcg): 15 studies[30-32,36-47]	6.53	—
Fentanyl dose (mcg): 15 studies[30-32,36-47]	—	21.17
Duration of surgery (min): 9 studies[36-39,41,43-46]	51.9	51.9

present at each hour of pain score assessment where the mean score was >3, and there was no response from the authors when clarification was sought. All studies analyzed participants in the groups to which they were randomized (Q9). No study reported any difference in the methods of outcome measurement between the groups (Q10). Eleven studies measured outcomes in a reliable way (Q11). Two studies[36,37] reported use of a VAS to assess sedation. The proposed outcome of both studies was to assess sedation, but the provided study definition of the measurement tool and its application were for a VAS and not a sedation scale. It is, therefore, unclear whether this is a language obstacle or whether the wrong method was used to assess the proposed outcome. The authors did not respond to requests for clarification.

Ten studies used appropriate statistical analysis (Q12). Two studies[31,37] did not provide the statistical tests employed for continuous data sourced during their trials, and a third study[32] did not state statistical tests employed for either continuous or dichotomous data sourced during the trial, but instead provided a test for a type of data that did not appear in the paper. Twelve studies had an appropriate trial design (Q13), while 1 study[32] described itself as a "comparative observational" study but employed methods more in keeping with an RCT.

In the 2 included cohort studies, it was not noted whether participants given rescue analgesia, especially those given a strong opioid,[47] were removed from further pain score assessments, and thus no clear strategy was provided about how confounding factors were addressed (Q4, Q5). In 1 study,[46] the number of participants who underwent pain score assessment was less than the number of participants recruited, with no explanation provided and follow-up could, therefore, not be considered complete (Q9, Q10). The authors did not respond to requests for clarification.

Characteristics of included studies

The characteristics of the included studies are provided in Appendix IV. All studies were in English between 2011 and 2022. Thirteen studies were RCTs[30-32,36-45] and 2 studies were prospective cohort studies.[46,47] A total of 1098 participants were included. Sample sizes were small, ranging from 40 to 130 participants mostly scheduled for elective CS. All participants were cared for in hospital settings. Table 3 summarizes the mean demographic characteristics in the intervention and comparator groups. There were insufficient data to pool regarding mean gestational age, body mass index, or dose of rescue analgesia required.

Standard postoperative analgesia was provided with combinations of nonopioid analgesics (paracetamol or ketorolac), a weak opioid (tramadol), and/or a strong opioid (pethidine). Similarly, rescue analgesia was provided with a range of pethidine, tramadol, ketorolac, or diclofenac. None of the studies that provided rescue analgesia with a strong opioid specified whether patients given rescue analgesia were removed from further pain score assessments.[30,38,47] Nine studies[30,36-39,43,44,46,47] stated the intention to report on postoperative pain scores at various intervals, but 2 studies[43,44] did not include the outcome data in their papers, with no response from the authors to a request make the data available. All studies reporting on pain scores stated the intention to use a VAS but in practice used an NPRS with the anchors 0

and 10, where 0 points indicated "no pain" and 10 points indicated "worst pain possible."[30,36-39,46,47] Eleven studies[31,32,36-38,41,43-47] documented an intention to report on duration of analgesia, but 2 studies[41,47] did not include the outcome data in their papers, with no response from the authors to a request to make the data available.

The duration of analgesia was defined as the time in minutes from drug administration to the first patient request for additional analgesia. All 10 studies intending to report on the duration of motor block provided the data in their papers.[30,36-41,43,46,47] The duration of motor block was defined as the time in minutes from motor block onset to full recovery of lower limb function as indicated by a score of 0 on a basic Bromage scale (0 = ability to move the hip, knee, and ankle; 1 = inability to move the hip but able to move the knee and ankle; 2 = inability to move the hip and knee but able to move the ankle; 3 = inability to move hip, knee, and ankle).

The most comparable side effects associated with intrathecal additive drug administration reported were hypotension, bradycardia, nausea and vomiting, pruritus, and shivering. These were measured by the number of patients who developed the side effects intraoperatively and/or postoperatively. None of the studies supplied a specific time frame during which side effects were recorded. The definitions of what was considered hypotension and bradycardia were provided in only 4 studies and are presented in Appendix IV.

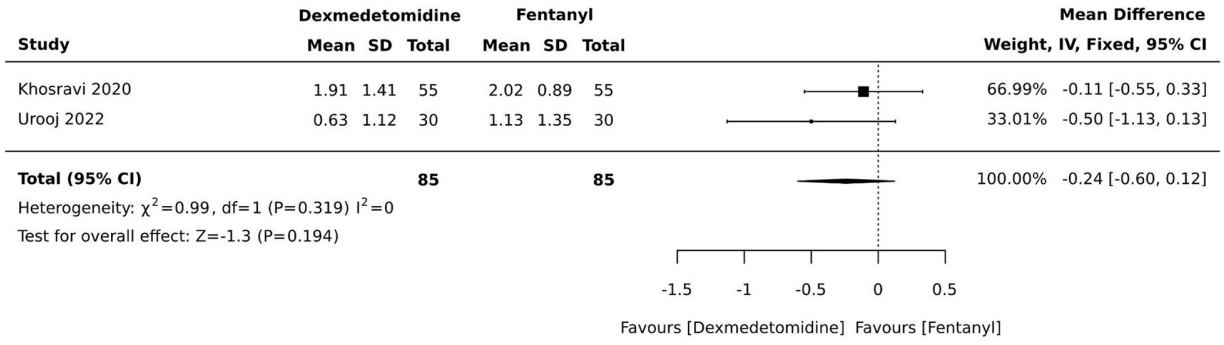
Review findings

Pain scores

Pain score at 1 hour postoperatively. There was moderate-certainty evidence for the pooled effect from 2 RCTs[38,39] with 170 participants that dexmedetomidine resulted in a lower NPRS score at 1 hour postoperatively; however, this was not statistically significant or meaningful. (Figure 2; MD 0.24 points lower, 95% CI 0.6 points lower to 0.12 points higher, P=0.19, I^2=0%). An MCID of 1 point on the NPRS (score range 0 to 10 points, where 0 points indicates "no pain" and 10 points indicates "worst pain possible") is often quoted for acute pain, but it has not been validated in the postoperative obstetric population.[48] Downgrading of the evidence was for risk of bias (Appendix III).

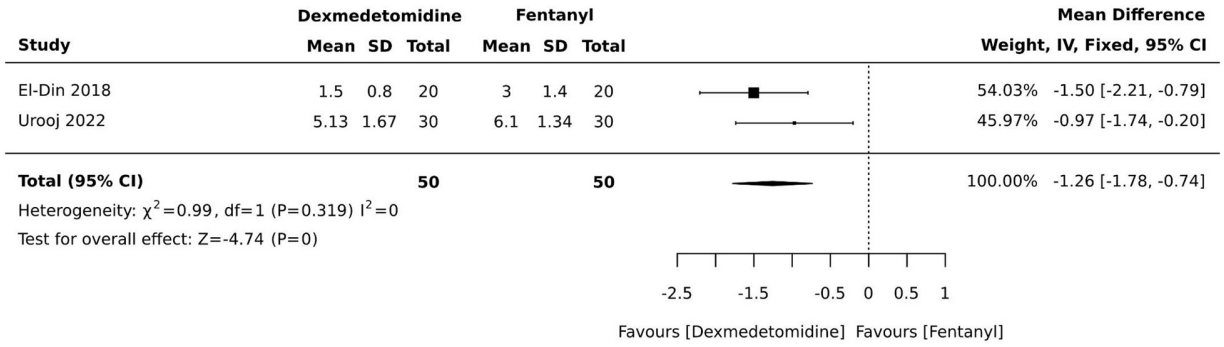
There was low certainty of evidence for the pooled effect from 2 non-RCTs[46,47] with 170 participants that dexmedetomidine resulted in a lower NPRS at 1 hour postoperatively (MD 0.28 points lower, 95% CI 0.53 to 0.03 points lower, P=0.03, I^2=0%). Although statistically significant, the result did not meet the MCID of 1 point and was, therefore, not meaningful. Downgrading of the evidence was for study design and risk of bias (Appendix III). Two RCTs[36,37] could not be pooled due to heterogeneity in outcome reporting, but they showed a significant between-group difference greater than the MCID of 1 point, with a lower NPRS with dexmedetomidine at 1 hour postoperatively. One RCT[30] showed no difference in pain score at 1 hour postoperatively, with the score in both groups

Figure 2: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine-fentanyl on pain scores at 1 hour postoperatively in patients undergoing Cesarean section under spinal anesthesia, as reported in 2 randomized controlled trials



IV, inverse variance
Pain was measured with a numeric pain rating scale. Scores ranged from 0 "no pain" to 10 "worst pain possible."

Figure 3: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine-fentanyl on pain scores at 4 hours postoperatively in patients undergoing Cesarean section under spinal anesthesia, as reported in 2 randomized controlled trials



IV, inverse variance
Pain was measured with a numeric pain rating scale. Scores ranged from 0 "no pain" to 10 "worst pain possible."

being 0. Due to low statistical heterogeneity, small sample sizes and unequal distribution of studies in subgroups, subgroup analyses, and sensitivity analyses were not performed for the pain scores at any hour.

Pain score at 4 hours postoperatively. There was moderate certainty of evidence for the pooled effect from 2 RCTs[30,39] with 100 participants that dexmedetomidine resulted in a lower NPRS at 4 hours that was greater than the MCID of 1 point (Figure 3; MD 1.26 points lower, 95% CI 1.78 to 0.74 points lower, P=0, I^2=0%). Downgrading of the evidence was for risk of bias (Appendix III). Two RCTs[36,37] and 1 non-RCT[47] could not be pooled due to heterogeneity in outcome reporting and study design. One RCT[36] found no difference in pain scores between dexmedetomidine and fentanyl at 4 hours, while the other RCT[37] and non-RCT[47] found a significant between-group difference greater than the MCID of 1 point at 4 hours.

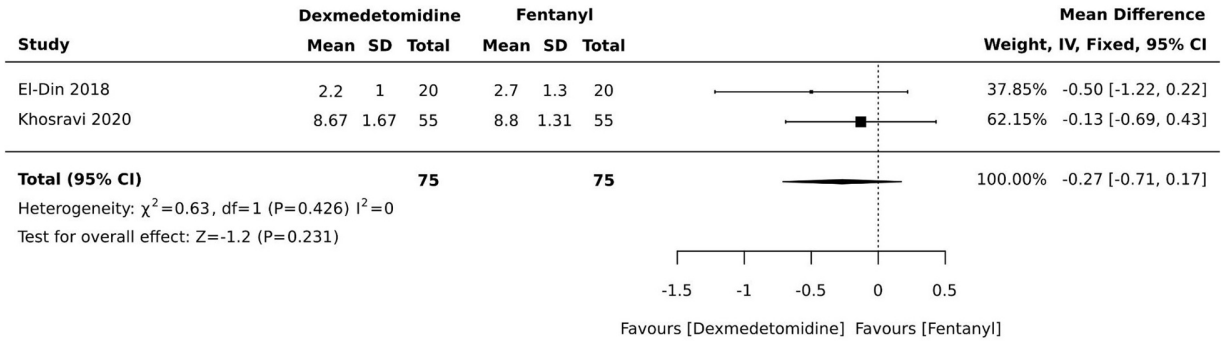
Pain score at 6 hours postoperatively. There was moderate certainty of evidence for the pooled effect from 2 RCTs[30,38] with 150 participants that dexmedetomidine resulted in a lower NPRS at 6 hours postoperatively. The result was not statistically significant and did not meet the MCID of 1 point. (Figure 4; MD 0.27 points lower, 95% CI 0.71 points lower to 0.17 points higher, P=0.23, I^2=0%). Downgrading of the evidence was for risk of bias (Appendix III). One non-RCT[46] could not be pooled due to heterogeneity in study design and found no significant between-group difference in NPRS at 6 hours postoperatively.

Pain scores after 6 hours postoperatively. One RCT[30] and 1 non-RCT[47] assessed pain scores after 6 hours postoperatively. The RCT showed a lower NPRS with dexmedetomidine at 8 hours of 1.2 points, which was greater than the MCID. There were no differences in NPRS at 12 and 16 hours. At 20 and 24 hours postoperatively, lower NPRS was again displayed with dexmedetomidine but both less than the MCID. The non-RCT showed lower NPRS in the dexmedetomidine group at 8 and 12 hours but both less than the MCID of 1 point.

Duration of analgesia

There was low-certainty evidence for the pooled effect from 8 RCTs[31,32,36-38,43-45] with 578 participants that dexmedetomidine provided a longer duration of analgesia measured in minutes compared with fentanyl (Figure 5; MD 93.30 minutes longer to first patient request for additional analgesia, 95% CI 62.40 to 124.19 minutes longer, P=0; I^2=98%). Downgrading of the evidence was done for risk of bias and inconsistency, with full details contained in the EP (Appendix III). The very high heterogeneity for the outcome must be noted, which lowers confidence in the exact amount of time by which dexmedetomidine can prolong the duration of analgesia. However, none of the studies included in the review that reported on the duration of analgesia showed

Figure 4: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine-fentanyl on pain scores at 6 hours postoperatively in patients undergoing Cesarean section under spinal anesthesia, as reported in 2 randomized controlled trials

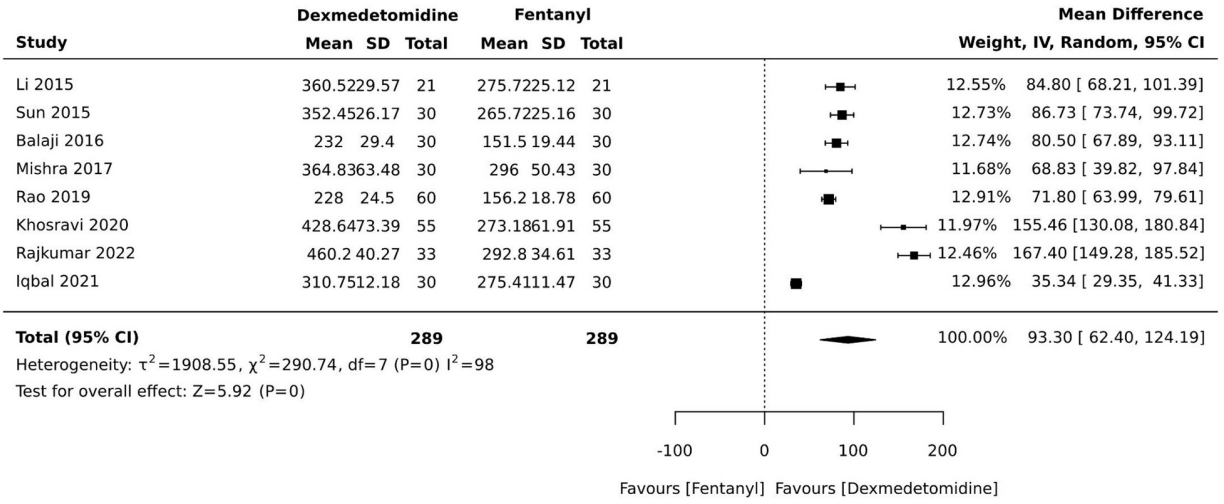


IV, inverse variance
Pain was measured with a numeric pain rating scale. Scores ranged from 0 "no pain" to 10 "worst pain possible."

a longer duration of analgesia with fentanyl. One non-RCT[46] was not pooled due to heterogeneity in study design and showed a longer duration of analgesia with dexmedetomidine that was statistically significant.

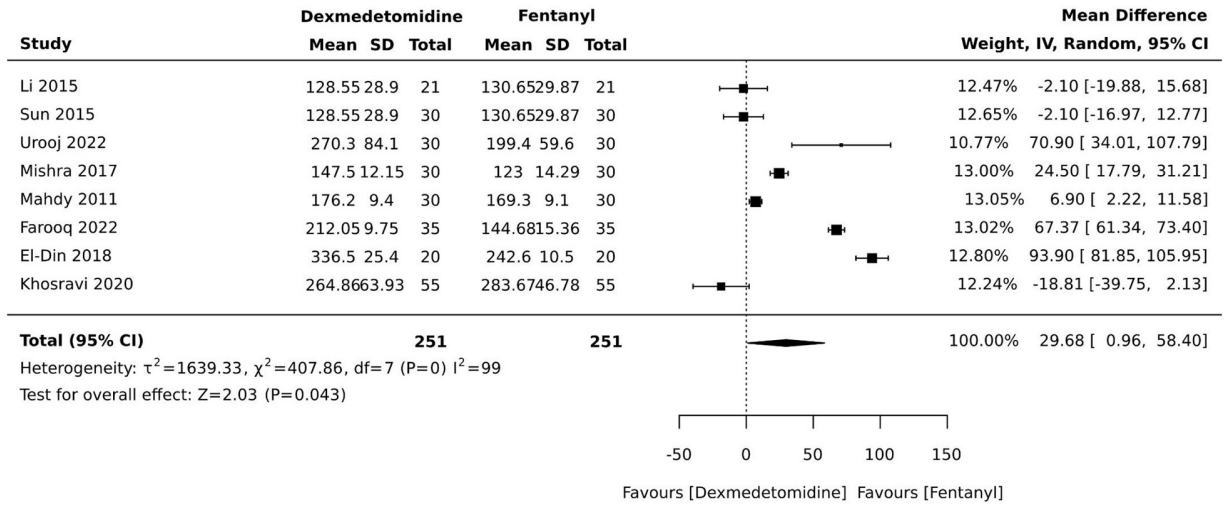
Subgroup analyses were employed to investigate very high statistical heterogeneity but did not provide any explanation that could be based on clinical or methodological differences in the pooled studies (Appendix V). It was hypothesized that higher doses of dexmedetomidine (>5 mcg) would result in a greater estimate of effect compared with lower doses (≤5 mcg), but subgroup analysis could not confirm this. The findings of subgroup analyses are limited by small sample sizes and unequal distribution of studies into groups that used higher and lower doses of dexmedetomidine (Appendix V). Sensitivity analysis was done by sequential removal of studies from meta-analysis and showed a duration of analgesia ranging from 82.38 minutes longer (95% CI 56.33 to 108.43

Figure 5: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine-fentanyl on the duration of analgesia in patients undergoing Cesarean section under spinal anesthesia, as reported in 8 randomized controlled trials



IV, inverse variance
Duration was measured by time in minutes to first patient request for additional analgesia.

Figure 6: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine-fentanyl on the duration of analgesia in patients undergoing Cesarean section under spinal anesthesia, as reported in 8 randomized controlled trials



IV, inverse variance
Duration was measured by time in minutes to full recovery of lower limb function.

minutes longer, P=0, I^2=97%; 512 participants) to 101.86 minutes longer (95% CI 71.78 to 131.93 minutes longer, P=0, I^2=97%; 518 participants).

The authors draw the reader's attention to the labeling of the forest plot since this is the only outcome in the review that requires inverse labeling (ie, where a longer duration is a desirable outcome). All other outcomes for this review are undesirable if they occur at a higher score, longer duration or greater incidence and, therefore, have traditional labeling of their forest plots.

Duration of motor block

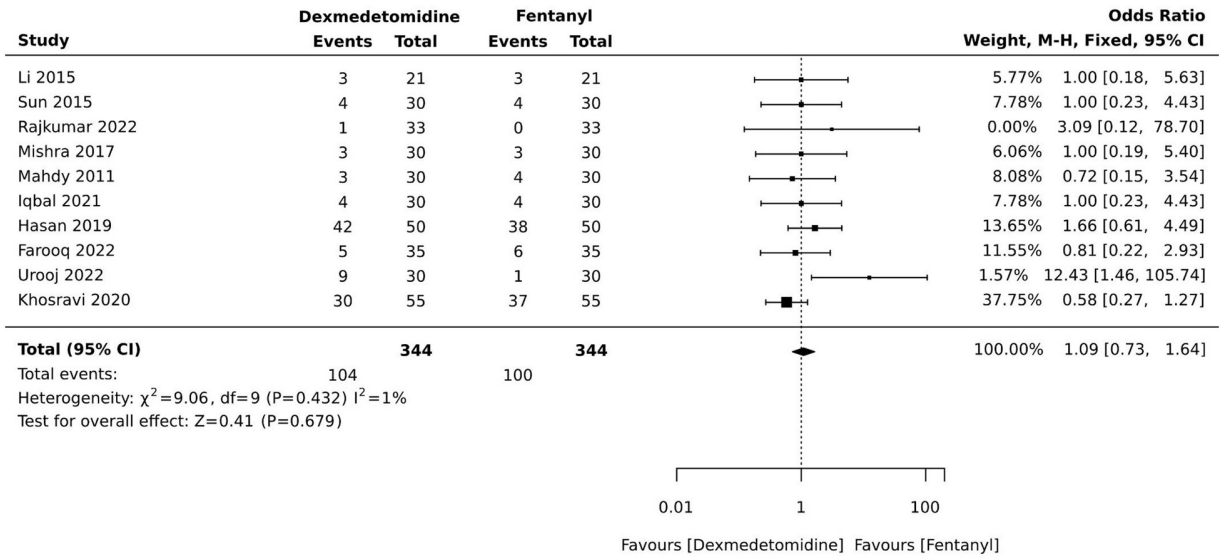
There was very low certainty of evidence for the pooled effect from 8 RCTs[30,36-41,43] (502 participants) that dexmedetomidine prolonged the duration of motor block measured in minutes compared with fentanyl (Figure 6; MD 29.68 minutes longer to full recovery of lower limb function, 95% CI 0.96 to 58.40 minutes longer, P=0.04, I^2=99%). Downgrading of the evidence was for risk of bias, inconsistency, and indirectness with full details contained in the EP (Appendix III). The very high heterogeneity for the outcome must be noted, which lowers confidence in whether dexmedetomidine increases the duration of motor block and the exact amount of time by which motor block can be prolonged. Two non-RCTs[46,47] with a total of 190 participants were pooled and delivered very low certainty of evidence that dexmedetomidine provided a longer duration of motor block. Downgrading for the pooled findings from the 2 non-RCTs was for study design, risk of bias, inconsistency, indirectness, and imprecision (Appendix III).

Subgroup analyses were employed to investigate statistical heterogeneity but did not provide any explanation that could be based on clinical or methodological differences in the pooled studies. It was hypothesized that higher doses of dexmedetomidine (doses >5 mcg) would result in a greater estimate of effect compared with lower doses (doses ≤5 mcg), but this could not be displayed in subgroup analysis of the studies included here. The findings of subgroup analyses are very limited by small sample sizes and unequal distribution of studies into groups that used higher and lower doses of dexmedetomidine (Appendix V). Sensitivity analysis was done by sequential removal of studies from meta-analysis and showed a duration of motor block ranging from 20 minutes longer (95% CI 5.10 minutes shorter to 45.11 minutes longer, P=0.12, I^2=98%; 462 participants) to 36.40 minutes longer (95% CI 7.02 to 65.78 minutes longer, P=0.02, I^2=99%; 392 participants).

Side effects

Hypotension. There was low certainty of evidence for the pooled effect from 10 RCTs[31,32,36-43] with

Figure 7: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine on the incidence of hypotension in patients undergoing Cesarean section under spinal anesthesia, as reported in 10 randomized controlled trials



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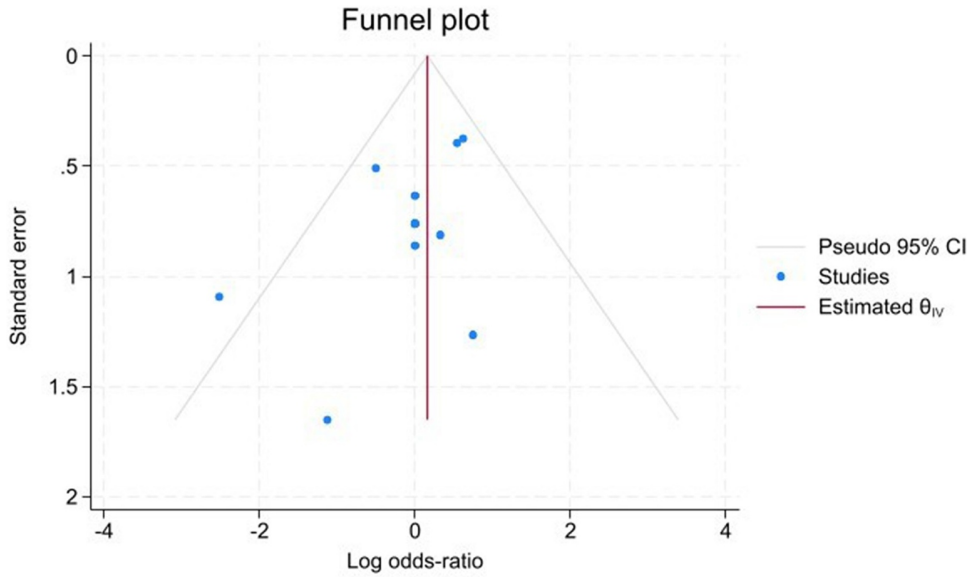
688 participants that dexmedetomidine increased the risk of hypotension compared with fentanyl. Hypotension was measured as the number of patients who developed hypotension at any time during surgery. Downgrading of the evidence was for risk of bias and imprecision (Appendix III). The absolute difference was a 2% increase in risk (95% CI 6% decrease to 11% increase in risk). Relative effects showed an increase in the risk of hypotension (Figure 7; odds ratio [OR] 1.09, 95% CI 0.73 to 1.64, P=0.68, I^2=1%). The result was not statistically significant. One non-RCT[46] was not pooled due to heterogeneity in study design and showed a decrease in the incidence of hypotension with dexmedetomidine that was not statistically significant. Due to low statistical heterogeneity, small sample sizes, and unequal distribution of studies in subgroups, subgroup analyses and sensitivity analyses were not performed for this outcome.

A funnel plot to assess publication bias was generated using STATA (Figure 8). The data from the outcome of hypotension was used, as this was the only outcome that had 10 or more contributing studies. Visual inspection of the funnel plot suggested possible asymmetry in study distribution at the base of the plot, indicating possible small-study effects. The regression-based Egger test was performed in STATA to investigate funnel plot asymmetry. The results yielded $\beta_1 = -1.34$, a standard error of 0.749, and a test statistic of $z = -1.85$ (P=0.06), indicating no significant small-study effects.

Bradycardia. There was low certainty of evidence for the pooled effect from 8 RCTs[31,36-40,42,43] with 558 participants that dexmedetomidine increased the risk of bradycardia compared with fentanyl. Bradycardia was measured as the number of patients who developed bradycardia at any time during surgery. Downgrading of the evidence was for risk of bias and imprecision (Appendix III). The absolute difference was a 2% increase in risk (95% CI 2% decrease to 8% increase in risk). Relative effects showed an increase in the risk of bradycardia (Figure 9; OR 1.22, 95% CI 0.66 to 2.27, P=0.53, I^2=0%). The result was not statistically significant. One non-RCT[46] was not pooled due to heterogeneity in study design and showed a decrease in the incidence of bradycardia with dexmedetomidine that was not statistically significant. Due to low statistical heterogeneity, small sample sizes, and unequal distribution of studies in subgroups, subgroup analyses and sensitivity analyses were not performed for this outcome.

Figure 8: Funnel plot assessing publication bias for meta-analysis comparing hyperbaric bupivacaine-dexmedetomidine with hyperbaric bupivacaine-fentanyl on the incidence of hypotension



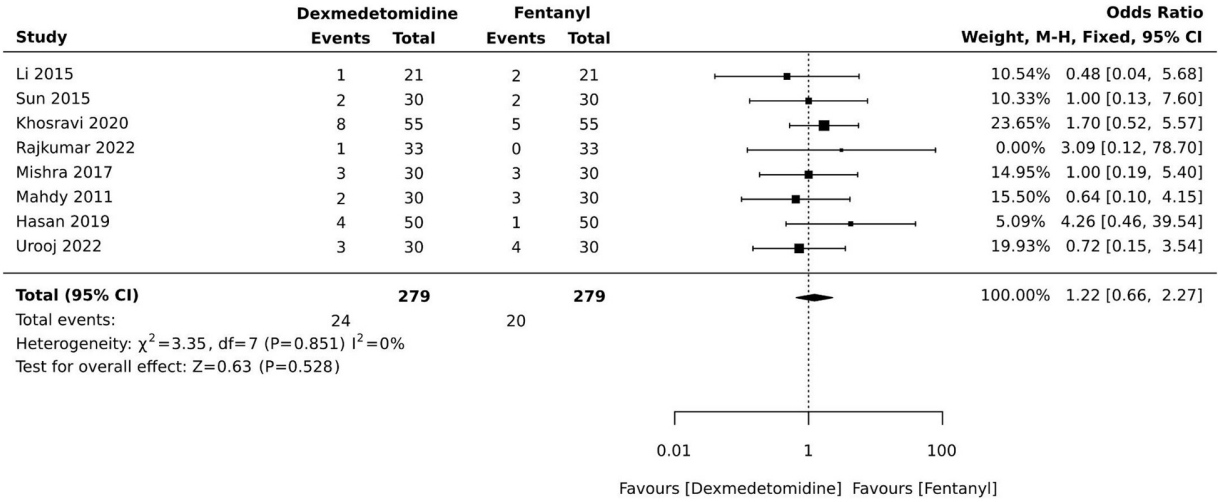
Each study included in the pooled analysis is represented by a blue dot, with small studies appearing at the base and larger studies at the apex of the funnel. The vertical red line indicates the log of the estimated overall odds ratio, and the gray diagonal lines represent the borders within which studies are expected to appear in the absence of bias.

Nausea and vomiting. There was moderate-certainty evidence for the pooled effect from 8 RCTs[31,32,36-38,40,42,43] with 558 participants that dexmedetomidine decreased the risk of nausea and vomiting as measured by the number of patients who developed intraoperative nausea and vomiting compared with fentanyl. Downgrading of the evidence was for risk of bias (Appendix III). The absolute difference was a 7% decrease in risk (95% CI 11% to 0% decrease in risk). Relative effects showed a decrease in the risk of nausea and vomiting (Figure 10; OR 0.57, 95% CI 0.34 to 0.97, P=0.04, I^2=0%). One RCT and 1 non-RCT were not pooled due to heterogeneity in outcome reporting and study design, respectively. The RCT[39] showed a statistically significant increase in the incidence of nausea with dexmedetomidine but a decrease in the incidence of vomiting with dexmedetomidine that was not statistically significant. The non-RCT[46] showed a decrease in the incidence of nausea and vomiting with dexmedetomidine that was not statistically significant. Due to low statistical heterogeneity, small sample sizes, and unequal distribution of studies in subgroups, subgroup analyses and sensitivity analyses were not performed for this outcome.

Pruritus. There was moderate certainty of evidence for the pooled effect from 7 RCTs[36,37,39,40,42-44] with 442 participants that dexmedetomidine decreased the risk of pruritus as measured by the number of patients who developed intraoperative pruritus compared with fentanyl. Downgrading of the evidence was for risk of bias (Appendix III). The absolute difference was an 11% decrease in risk (95% CI 11% to 9% decrease in risk). Relative effects showed a decrease in risk of pruritus (Figure 11; OR 0.06, 95% CI 0.02 to 0.22, P=0, I^2=48%). Due to low statistical heterogeneity, small sample sizes, and unequal distribution of studies in subgroups, subgroup analyses and sensitivity analyses were not performed for this outcome.

Shivering. There was moderate certainty of evidence for the pooled effect from 5 RCT[32,37-39,42] with 390 participants that dexmedetomidine decreased the risk of shivering as measured by the number of patients who developed intraoperative shivering compared with fentanyl. Downgrading of the evidence was for risk of bias (Appendix III). The absolute difference was an 8% decrease in risk (95% CI 9% to 3% decrease in risk). Relative effects showed a decrease

Figure 9: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine on the incidence of bradycardia in patients undergoing Cesarean section under spinal anesthesia, as reported in 8 randomized controlled trials



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in the risk of shivering (Figure 12; OR 0.28, 95% CI 0.12 to 0.65, P=0.003, I^2=0%). One non-RCT[46] was not pooled due to heterogeneity in study design and showed a decrease in the incidence of shivering with dexmedetomidine. Due to low statistical heterogeneity, small sample sizes, and unequal distribution of studies in subgroups, subgroup analyses and sensitivity analyses were not performed for this outcome.

Discussion

Multimodal analgesia is the current standard of care recommended in ERAC protocols.[11] Neuraxial administration of drugs capable of providing long-lasting pain relief is an important component of such protocols. Postoperative pain is commonly assessed using a pain score, but it is not as simple as comparing

Figure 10: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine on the incidence of nausea and vomiting in patients undergoing Cesarean section under spinal anesthesia, as reported in 8 randomized controlled trials

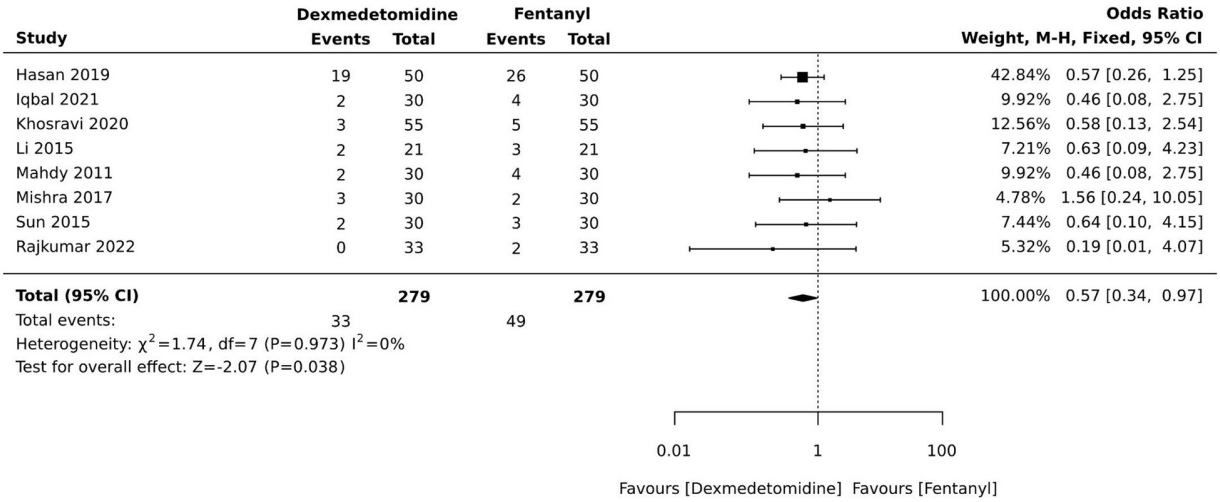

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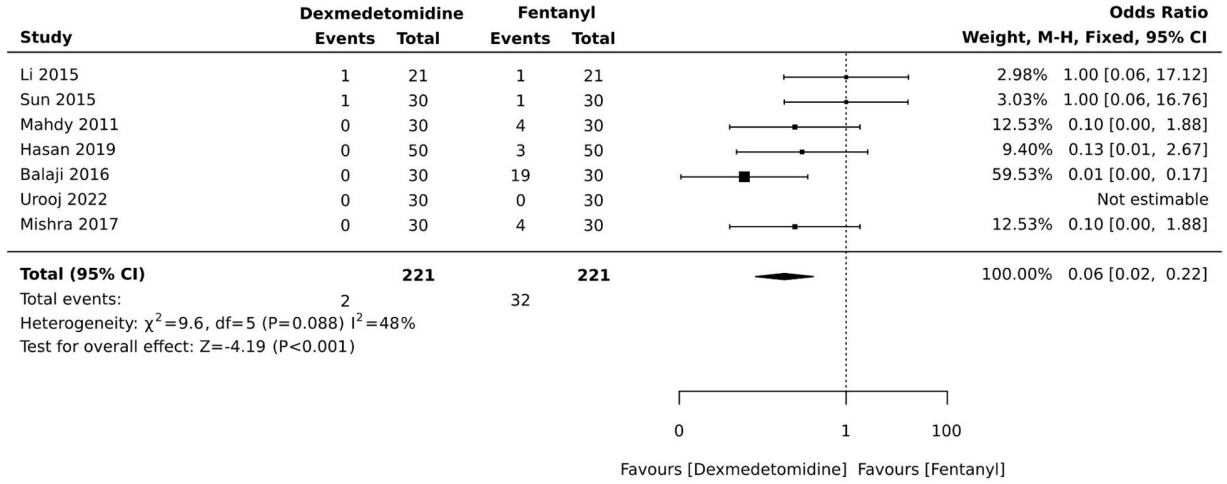
Figure 11: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine on the incidence of pruritus in patients undergoing Cesarean section under spinal anesthesia, as reported in 7 randomized controlled trials



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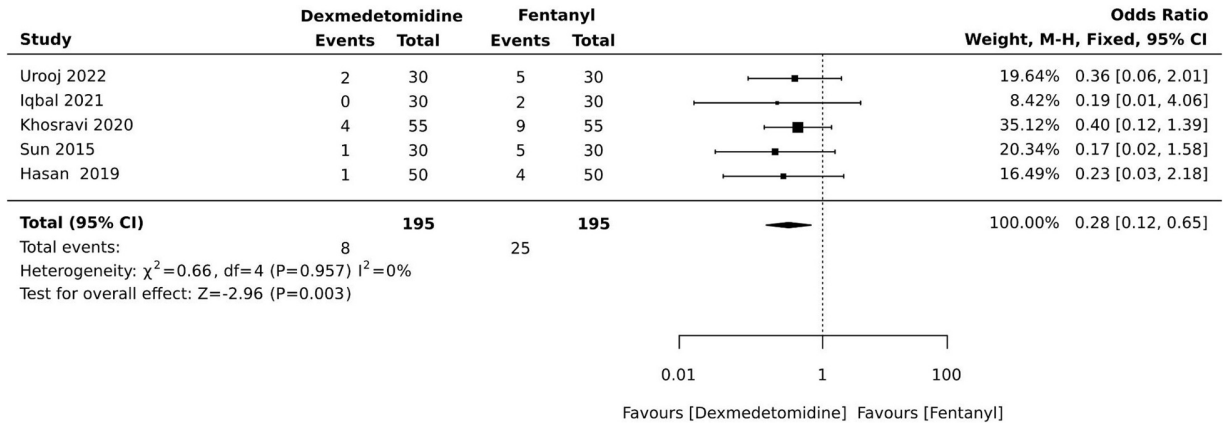
numbers. Kleinman *et al.*[49] and Lester *et al.*[50] both performed before-and-after studies after implementation of an ERAC protocol and found that, although postoperative opioid consumption in the ERAC group was lower, there was no clinically significant difference in pain scores between the groups. This suggests that pain scores in isolation might not be adequate to inform decisions about analgesic superiority and underlines the fact that pain management should not be limited to pharmacological strategies. In our review, we found that dexmedetomidine resulted in lower NPRS scores at 1, 4, and 6 hours postoperatively, but only the reduction in NPRS score at 4 hours postoperatively was clinically significant. As pain

Figure 12: The effect of hyperbaric bupivacaine-dexmedetomidine compared with hyperbaric bupivacaine on the incidence of shivering in patients undergoing Cesarean section under spinal anesthesia, as reported in 5 randomized controlled trials



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scores can be misleading, these results would have been better interpreted in the presence of data about associated opioid sparing.

A systematic review by La Via *et al.*[51] compared intrathecal α_2 agonists (dexmedetomidine 5 to 10 mcg or clonidine 50 to 75 mcg) to fentanyl (15 to 25 mcg) when added to either hyperbaric or isobaric bupivacaine in patients undergoing CS. La Via *et al.*[51] found a low level of evidence that dexmedetomidine prolongs the time to first request for additional analgesia compared with fentanyl by 85.9 minutes (95% CI 23.8 to 147.9 minutes longer). La Via *et al.*[51] also demonstrated a marginal increase in duration of motor block by 1.7 minutes (95% CI 19.2 minutes shorter to 22.5 minutes longer) and a lower incidence of nausea and vomiting, shivering, and pruritus with intrathecal α_2 agonists compared with intrathecal fentanyl. In our review we found that dexmedetomidine prolonged the time to first request for additional analgesia and reduced the incidence of nausea and vomiting, pruritus, and shivering but at the expense of an increase in the incidence of hypotension, bradycardia, and a longer duration of motor block. Similarly, a systematic review by Qian *et al.*[52] compared epidural administration of dexmedetomidine and fentanyl as additives to ropivacaine for anesthesia for lower abdominal surgeries and orthopedic lower limb surgeries. The authors found that dexmedetomidine prolongs the time to first request for additional analgesia compared with fentanyl by 99.13 minutes (95% CI 82.89 to 115.37 minutes longer), with decreased incidence of nausea and vomiting and shivering but an increased incidence of oral dryness.

All studies included in our review were conducted in low- and middle-income countries (LMICs). In such countries, drug supply shortages are common, and awareness of suitable alternatives can ensure resilience in the delivery of essential services to pregnant patients requiring operative delivery. Dexmedetomidine has a contract price 20 times higher than fentanyl for the same amount of drug in micrograms based on South African data,[53] creating doubt about its feasible widespread use in LMICs until more affordable generic alternatives become available. Unfamiliarity with dexmedetomidine and the fact that administration via the intrathecal route is still an evolving practice are also likely to limit its use in LMIC.

While the intrathecal administration of drugs with the potential to provide long-lasting analgesia, such as dexmedetomidine, provides a valuable contribution to postoperative pain management, especially in resource and staff constrained settings, it does not negate the need for multimodal management of postoperative pain. Kintu *et al.*[54] demonstrated that different analgesic agents might be more effective at different times in the postoperative period. Bollag and Nelson[55] pointed out that adequate pain control is not so much a target of enhanced recovery but rather an important prerequisite for it.

Strengths

The strengths of this review include a well-defined review question; an extensive search for eligible papers that included unpublished literature, such as theses; and independent screening, selection, and critical appraisal of eligible studies by 2 reviewers. Comparative assessment of analgesic efficacy was performed using 2 independent outcome measures (pain score and time to first request for additional analgesia) to lend robustness to the primary outcome of analgesic efficacy. As pain is only 1 factor affecting post-CS recovery, the evaluation of side-effect profiles provides a more comprehensive comparison between dexmedetomidine and fentanyl when used as intrathecal additives.

Limitations

The overall methodological quality of the studies included was moderate. Further limitations of the included studies were small sample sizes ranging from 40 to 130 participants and incomplete or unclear study information, with limited responses from authors to supply or clarify the study information in question. All studies included in the review were conducted in LMICs, potentially limiting the population-based applicability of the study findings. The limitations of assessing pain control with pain scores was discussed previously. Unfortunately, there were insufficient data to pool to compare opioid consumption in the fentanyl and dexmedetomidine groups.

Limitations of the review process were that dose ranges were compared instead of a specific dose of dexmedetomidine to a specific dose of fentanyl when added to a specific dose of hyperbaric bupivacaine. Another limitation was the use of an arbitrary scoring system with no specific weight to any of the critical appraisal questions. The wide variance in point estimates for duration of analgesia was largely unexplained except perhaps by the wide interindividual

and cultural variability in the perception and expression of pain.[56] Similarly, the subjectivity in assessment of motor function as measured with the Bromage score could account for the same phenomenon observed in the duration of motor block. La Via *et al*.[51] and Qian *et al*.[52] encountered similarly high heterogeneity in pooling results for duration of analgesia and duration of motor block. The findings of subgroup analyses were limited by small sample sizes and uneven distribution of studies across subgroups and, therefore, cannot be used to draw any reliable conclusions. The authors' misunderstanding that retrospective cohort studies are not suited to investigate the review question was also a potential weakness. No eligible studies had retrospective designs, however, and thus no evidence was overlooked on this account.

Conclusions

The evidence from this review suggests that dexmedetomidine probably results in a longer duration of analgesia and a meaningfully lower NPRS score limited to the fourth hour postoperatively. Dexmedetomidine also probably results in lower incidence of nausea and vomiting, pruritus, and shivering. Dexmedetomidine may increase the incidence of hypotension and bradycardia. The evidence is uncertain about whether dexmedetomidine results in a longer duration of motor block.

Recommendations for practice

The findings of the review suggest that intrathecal dexmedetomidine may have a role in enhancing recovery after CS, but there is currently insufficient evidence to recommend routine use of dexmedetomidine as an additive to hyperbaric bupivacaine for patients presenting for CS. Based on the JBI Grades of Recommendation,[57] a grade B or "weak" recommendation for its use is given.

Recommendations for research

Future research should focus on high-quality RCTs with complete descriptions regarding study design, especially blinding of participants and outcome assessors, clear definitions of study outcomes and how they will be measured, and adequate reporting of pharmacological and non-pharmacological measures employed as standard and rescue analgesia. Consideration can be given to measurement of analgesic efficacy through comparative opioid consumption as administered through patient-controlled analgesia devices. This would remove the bias introduced by participants being unwilling or hesitant to report and quantify their pain. Another comparison of the overall efficacy of intrathecal dexmedetomidine can be studied through comparison of obstetric quality of recovery scores, such as the ObsQoR-11 score.[58]

Acknowledgments

The University of Witwatersrand Health Science Research Office for funding to attend the JBI Comprehensive Systematic Review Training Program and for providing access to STATA. WH Boshoff for support and statistical assistance.

This review will contribute toward a master of medicine in anesthesia for JB.

Funding

Funding was provided by the University of Witwatersrand Health Science Research Office for JB and KP to attend the JBI Comprehensive Systematic Review Training Program. The funder had no involvement in the conduct of the review.

Declarations

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

Author contributions

The review was conceptualized by JB in collaboration with MF, KP, and PM. The manuscript was drafted by JB and critically reviewed by MF, KP, and PM.

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Appendix I: Search strategy

Cochrane Central Register of Controlled Trials (EBSCOhost)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	([mh "cesarean section"] OR caesarean section):ti,ab,kw (Word variations have been searched)	15,783
#2	([mh "bupivacaine"] OR bupivacaine):ti,ab,kw (Word variations have been searched)	17,201
#3	([mh "dexmedetomidine"] OR dexmedetomidine):ti,ab,kw (Word variations have been searched)	9507
#4	([mh "fentanyl"] OR fentanyl):ti,ab,kw (Word variations have been searched)	19,822
#5	#1 AND #2 AND #3 AND #4	33

PubMed (EBSCOhost)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	(cesarean section[MeSH Terms]) OR (caesarean section[Text Word])	67,999
#2	(bupivacaine[MeSH Terms]) OR (bupivacaine[Text Word])	18,878
#3	(dexmedetomidine[MeSH Terms]) OR (dexmedetomidine[Text Word])	9559
#4	(fentanyl[MeSH Terms]) OR (fentanyl[Text Word])	29,145
#5	#1 AND #2 AND #3 AND #4	13

Scopus (EBSCOhost)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	TITLE-ABS-KEY (cesarean AND section)	129,848
#2	TITLE-ABS-KEY (bupivacaine)	43,587
#3	TITLE-ABS-KEY (dexmedetomidine)	18,371
#4	TITLE-ABS-KEY (fentanyl)	79,893
#5	#1 AND #2 AND #3 AND #4	55

Embase (Ovid)		
Search conducted: May 27, 2024		
Search	**Query**	**Records retrieved**
#1	(caesarean section.ti. or cesarean section.af.) and intrathecal.af. and dexmedetomidine.af.	88

ClinicalTrials.gov (Ovid)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	Condition/disease: cesarean section	6
	Other terms: bupivacaine	
	Intervention/ treatment: dexmedetomidine AND fentanyl	

WHO ICTRP (Ovid)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	cesarean section AND bupivacaine AND dexmedetomidine AND fentanyl	6

Google Scholar (Ovid)		
Search conducted: May 20, 2024		
Search	**Query**	**Records retrieved**
#1	(cesarean section) AND bupivacaine AND dexmedetomidine AND fentanyl	7420 Records on first 20 pages: 200

Appendix II: Studies ineligible following full-text review

1. Deotale A, Kadam S. Comparison of intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine: a randomised controlled trial. J Clin Diagn Res 2021;15(8):16-9.

   Reason for exclusion: Ineligible participant characteristics

2. El-Din TN, Hussien M, El-Galil A, Ellatif AE. Intrathecal fentanyl versus dexmedetomedine as adjuvants to bupivacaine for cesarean section. Int J Med Arts 2021;3(1):1083-7.

   Reason for exclusion: Duplicate study under Creative Commons License

3. La Via L, Santonocito C, Bartolotta N, Lanzafame B, Morgana A, Continella C, *et al*. α-2 agonists vs. fentanyl as adjuvants for spinal anesthesia in elective cesarean section: a meta-analysis. Minerva Anestesiol 2023;89(5):445-54.

   Reason for exclusion: Ineligible intervention and comparator

4. Li X-X, Li Y-M, Lv X-L, Wang X-H, Liu S. The efficacy and safety of intrathecal dexmedetomidine for parturients undergoing cesarean section: a double-blind randomized controlled trial. BMC Anesthesiol 2020;20(1):190.

   Reason for exclusion: Incomplete study information – unclear whether isobaric or hyperbaric bupivacaine was used, with no response from authors.

5. Shen QH, Li HF, Zhou XY, Yuan XZ, Lu YP. Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis. J Int Med Res 2020;48(5):1-13.

   Reason for exclusion: Ineligible comparator

6. Zafar M, Zeeshan U, Sher SJ, Rizwan AS, Fatima A. Comparison of dexmedetomidine and fentanyl as adjuvants to intrathecal levobupivacaine in lower segment cesarean section. Pak J Med Health Sci 2021;15(8):2537-41.

   Reason for exclusion: Incomplete study information – unclear whether isobaric or hyperbaric bupivacaine was used, with no response from authors.

Appendix III: Evidence profile

Question: Should dexmedetomidine be used instead of fentanyl as an additive to hyperbaric bupivacaine for Cesarean section?

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Pain score at 1 hour post CS (assessed with NPRS; scale from 0 to 10)												
2	Randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	85	85	—	MD **0.24 points lower** (0.60 lower to 0.12 higher)	⊕⊕⊕◯ Moderate	IMPORTANT Dexmedetomidine probably results in a lower but not meaningful reduction in NPRS at 1 hour post CS

a) Concern for serious risk of bias, as data for this outcome were sourced from studies with moderate (n=1) and low (n=1) risk of bias
b) No wide variation of points estimates; CIs overlapped and low I^2
c) The CI included no effect; intervals on both sides were less than the MCID of 1 point; OIS for MD 0.24 points is 112 participants, which is less than 170 participants for this outcome
d) Publication bias could not be assessed for this outcome

CS, Cesarean section; MCID, minimum clinically important difference; MD, mean difference; NPRS, numeric pain rating scale; OIS, optimal information size

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Pain score at 1 hour post CS (assessed with NPRS; scale from 0 to 10)												
2	Non-randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	85	85	-	MD **0.28 points lower** (0.58 lower to 0.03 lower)	⊕⊕◯◯ Low	IMPORTANT Dexmedetomidine may result in a lower but not meaningful reduction in NPRS at 1 hour post CS

a) Concern for serious risk of bias, as data for this outcome were sourced from studies with moderate (n=1) and low (n=1) risk of bias
b) No wide variation of points estimates; CIs overlapped and low I^2
c) The CI excluded no effect; intervals on both sides were less than the MCID of 1 point; OIS for MD 0.28 points is 118 participants, which is less than 170 participants for this outcome
d) Publication bias could not be assessed for this outcome

CS, Cesarean section; MCID, minimum clinically important difference; MD, mean difference; NPRS, numeric pain rating scale; OIS, optimal information size

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance What happens
Pain score at 4 hours post CS (assessed with NPRS; scale from 0 to 10)												
2	Randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	50	50	-	MD **1.26 points lower** (1.78 lower to 0.74 lower)	⨁⨁⨁◯ Moderate	IMPORTANT Dexmedetomidine probably results in a meaningful reduction in NPRS at 4 hours post CS

a) Concern for serious risk of bias as data for this outcome was sourced from studies with moderate (n=1) and low (n=1) risk of bias
b) No wide variation of points estimates; CIs overlapped and low I^2
c) CI excludes no effect and point estimate greater than MCID of 1 point; OIS for MD 1.26 points is 46 participants, which is less than 100 participants for this outcome.
d) Publication bias could not be assessed for this outcome

CS, Cesarean section; MCID, minimum clinically important difference; MD, mean difference; NPRS, numeric pain rating scale; OIS, optimal information size

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance What happens
Pain score at 6 hours post CS (assessed with NPRS; scale from 0 to 10)												
2	Randomized trials	Not serious[a]	Not serious[b]	Not serious	Serious[c]	None[d]	75	75	-	MD **0.27 points lower** (0.71 lower to 0.17 higher)	⨁⨁⨁◯ Moderate	IMPORTANT Dexmedetomidine probably results in a lower but not meaningful reduction in NPRS at 6 hours post CS

a) No concern for serious risk of bias as data for this outcome were sourced from studies at low (n=2) risk of bias
b) No wide variation of points estimates; CIs overlapped and low I^2
c) The CI included no effect; intervals on both sides were less than the MCID of 1 point; OIS for MD 0.27 is 4206 participants, which is more than 150 participants for this outcome
d) Publication bias could not be assessed for this outcome

CS, Cesarean section; MCID, minimum clinically important difference; MD, mean difference; NPRS, numeric pain rating scale; OIS, optimal information size

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance What happens
Duration of analgesia (assessed with time in minutes to first request for additional analgesia)												
8	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious[c]	None[d]	289	289	-	**MD 93.30 minutes more** (62.40 minutes more to 124.19 minutes more)	⊕⊕◯◯ Low	IMPORTANT Dexmedetomidine may result in a longer duration of analgesia

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=5) and low (n=3) risk of bias
b) Wide variance in point estimates and considerable I^2 value all likely to lower confidence in estimate of effect. All studies demonstrated a longer duration of analgesia with dexmedetomidine, unlike for the outcome duration of motor block, where different studies showed both a longer and a shorter duration of block with dexmedetomidine. For this reason, the authors decided to downgrade only 1 level for inconsistency.
c) The CI excluded no effect; MCID is unknown but participants 578 greater than "rule of thumb" 400 participants
d) Publication bias could not be assessed for this outcome

MCID, minimum clinically important difference; MD, mean difference

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance What happens
Duration of motor block (assessed with time in minutes to Bromage score of 0)												
8	Randomized trials	Serious[a]	Very serious[b]	Serious[d]	Not serious[c]	None[e]	251	251	-	**MD 29.68 minutes more** (0.96 minutes more to 58.40 more)	⊕◯◯◯ Very low	IMPORTANT The evidence is uncertain whether dexmedetomidine results in a longer duration of motor block

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=3) and low (n=5) risk of bias
b) Wide variance in point estimates and considerable I^2 value likely to lower confidence in estimate of effect
c) The CI excluded no effect; MCID is unknown but participants 502 greater than "rule of thumb" 400 participants
d) Bromage score was used as a surrogate measurement since time to full motor block resolution was determined as time to reach a Bromage score of 3
e) Publication bias could not be assessed for this outcome

MCID, minimum clinically important difference; MD, mean difference

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Hypotension												
10	Randomized trials	Serious[a]	Not serious[b]	Not serious	Serious	None[d]	102/344 (29.7%)	99/344 (28.8%)	**OR 1.09** (0.73 to 1.64)	**2 more per 100** (from 6 fewer to 11 more)	⊕⊕◯◯ Low	IMPORTANT Dexmedetomidine may increase the incidence of hypotension

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=6) and low (n=4) risk of bias
b) No wide variance in point estimates, low I^2 value, CIs overlap
c) The CI includes no effect; OIS for the above event rate requires 8176 participants, which is more than the 688 participants for this outcome
d) Publication bias not detected for this outcome

OIS, optimal information size; OR, odds ratio

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Bradycardia												
8	Randomized trials	Serious[a]	Not serious[b]	Not serious	Serious[c]	None[d]	24/279 (8.6%)	20/279 (7.2%)	**OR 1.22** (0.66 to 2.27)	**1 more per 100** (from 2 fewer to 8 more)	⊕⊕◯◯ Low	IMPORTANT Dexmedetomidine may increase the incidence of bradycardia

a) Concern for serious risk of bias as data for this outcome ere sourced from studies at moderate (n=4) and low (n=4) risk of bias
b) No wide variance in point estimates, low I^2 value, CIs overlap
c) The CI includes no effect; OIS for the above event rate requires 2746 participants, which is more than the 558 participants for this outcome
d) Publication bias could not be assessed for this outcome

OIS, optimal information size; OR, odds ratio

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Nausea and vomiting												
8	Randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	33/279 (11.8%)	49/279 (17.6%)	**OR 0.57** (0.34 to 0.97)	**7 fewer per 100** (from 11 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT Dexmedetomidine probably results in a lower incidence of nausea and vomiting

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=4) and low (n=4) risk of bias
b) No wide variance in point estimates, low I^2 value, CIs overlap
c) The CI excludes no effect; OIS for the above event rate requires 422 participants, which is less than the 558 participants for this outcome
d) Publication bias could not be assessed for this outcome

OIS, optimal information size; OR, odds ratio

Certainty assessment							No of patients		Effect		Certainty	Importance What happens
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)		
Pruritus												
7	Randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	5/221 (2.3%)	25/221 (11.3%)	**OR 0.06** (0.02 to 0.22)	**11 fewer per 100** (from 11 fewer to 9 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT Dexmedetomidine probably results in a lower incidence of pruritus

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=4) and low (n=3) risk of bias
b) No wide variance in point estimates, majority of CIs overlap, substantial I^2 value but likely due to differences in comparator drug doses
c) The CI excludes no effect; OIS for the above event rate requires 98 participants, which is less than the 442 participants for this outcome
d) Publication bias could not be assessed for this outcome

OIS, optimal information size; OR, odds ratio

Certainty assessment							No of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomdine	Fentanyl	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance What happens
Shivering												
5	Randomized trials	Serious[a]	Not serious[b]	Not serious	Not serious[c]	None[d]	12/195 (6.2%)	21/195 (10.8%)	**OR 0.28** (0.12 to 0.65)	**8 fewer per 100** (from 9 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT Dexmedetomidine probably results in a lower incidence of shivering

a) Concern for serious risk of bias as data for this outcome were sourced from studies at moderate (n=3) and low (n=2) risk of bias
b) No wide variance in point estimates, CIs overlap, low I^2
c) The CI excludes no effect; OIS for the above event rate requires 180 participants, which is less than the 390 participants for this outcome
d) Publication bias could not be assessed for this outcome

OIS, optimal information size; OR, odds ratio

Appendix IV: Characteristics of included studies

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
Balaji 2016[44] India	RCT Moderate	Sample: 60 Included: • ASA I and II • GA ≥36 weeks • BMI not specified • Singleton pregnancies • Age 18-35 years • Elective Excluded: • Cardiac, liver, kidney, neurological disease • Gestational hypertension • Gestational diabetes Additional postoperative analgesia: • Standard—tramadol 100 mg IM stat • Rescue—diclofenac 75 mg IM	Volume 2.0 mL HB 0.5% 7.5 mg DEX 5 mcg	Volume 2.0 mL HB 0.5% 7.5 mg FEN 25 mcg	1. Postoperative pain score at 1, 2, 3, 4, 5, 6 hours 2. Duration of analgesia 3. Nausea 4. Vomiting 5. Pruritus	1. Data not provided 2. Longer in BD* 3. Inappropriate descriptive statistic used 4. Inappropriate descriptive statistic used 5. Less in BD*
El-Din *et al*. 2018[30] Egypt	RCT Low	Sample: 40 Included: • ASA I and II • GA not specified • Fetus per pregnancy not specified • BMI ≤30 • Elective CS • Emergency CS Excluded: • BMI ≥30 Additional analgesia: • Standard—ketorolac IV x 6 hourly • Rescue—pethidine 20 mg IV	Volume 2.5 mL HB 0.5% 10 mg DEX 10 mcg	Volume 2.5 mL HB 0.5% 10 mg FEN 20 mcg	1. Postoperative pain score at 1, 2, 4, 6, 8, 12, 16, 20, 24 hours 2. Duration of motor block	1. Less in BD at 1, 2,* 4,* 6, 8, 20, 24 hours; ND at 12, 16 hours 2. Longer in BD*
Farooq *et al*. 2022[41] Pakistan	RCT Moderate	Sample: 70 Included: • ASA not specified • GA not specified • BMI not specified • Number of fetuses not specified • Age 20-30 years • Urgency not specified	Volume not specified HB 0.75% 12 mg DEX 10 mcg	Volume not specified HB 0.75% 12 mg FEN 15 mcg	1. Duration of analgesia 2. Duration of motor block 3. Hypotension (no supplied study definition) 4. Nausea	1. Data not provided 2. Longer in BD* 3. Less in BD 4. ND

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
		Excluded: • Cardiopulmonary, cerebrovascular, hepatic and renal disease • Diabetes mellitus • Spinal deformities • Anticoagulant therapy Additional analgesia: • Standard—not specified • Rescue—nalbuphine 10 mg IV; paracetamol 1 g IV				
Hasan *et al.* 2019[42] India	RCT Moderate	Sample: 100 Included: • ASA I and II • GA not specified • BMI specified • Number of fetuses not specified • Age 18-32 years • Elective surgery Excluded: • Emergency surgery Additional analgesia: • Not specified	Volume not specified HB 0.5% 10 mg DEX 5 mcg	Volume not specified HB 0.5% 10 mg FEN 12.5 mcg	1. Hypotension (no supplied study definition) 2. Bradycardia (no supplied study definition) 3. Nause and vomiting 4. Shivering 5. Pruritus	1. More in BD 2. More in BD 3. Less in BD 4. Less in BD 5. More in BD
Iqbal *et al.* 2021[32] Pakistan	RCT Moderate	Sample: 60 Included: • ASA not specified • GA not specified • BMI not specified • Number of fetuses not specified • Age not specified • Urgency of surgery not specified Excluded: • Eclampsia • Preeclampsia • Diabetes Additional analgesia: • Not specified	Volume not specified HB 0.5% 12.5 mg DEX 5 mcg	Volume not specified HB 0.5% 12.5 mg FEN 25 mcg	1. Duration of analgesia 2. Hypotension (no supplied study definition) 3. Nausea and vomiting 4. Shivering	1. Longer in BD 2. ND 3. Less in BD 4. Less in BD

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
Khosravi *et al*. 2020[38] Iran	RCT Low	Sample: 110 Included: • ASA I and II • Fetus per pregnancy not specified • GA ≥ 37 weeks • Elective CS Excluded: • Valvular heart disease • Placenta praevia Additional analgesia: • Standard: not specified • Rescue: pethidine 25 mg IV	Volume 2.5mL HB 0.5% 10 mg DEX 5 mcg	Volume 2.5 mL HB 0.5% 10 mg FEN 25 mcg	1. Postoperative pain score at 0, 1, 3, 6 hours 2. Duration of analgesia 3. Duration of motor block 4. Hypotension (SBP < 90 mmHg or >20% decrease in MAP from baseline) 5. Bradycardia (HR < 50 bpm) 6. Nausea and vomting 7. Shivering	1. Lower in BD at 0,* 1, 3, 6 hours 2. Longer in BD* 3. Shorter in BD 4. Less in BD 5. More in BD 6. Less in BD 7. Less in BD
Li *et al*. 2015[36] China	RCT Low	Sample: 42 Included: • ASA I and II • GA 36- 40 weeks • Singleton pregnancies • BMI not specified • Elective • Ages 20-35 years Excluded: • PET • Multiple gestation Additional analgesia: • CSE technique described but no epidural or analgesia via any other route ot specified	Volume 4 mL HB 10 mg (concentration not specified) DEX 10 mcg	Volume 4 mL HB 10 mg (concentration not specified) FEN 15 mcg	1. Postoperative pain score at 1, 2, 4 hours 2. Duration of analgesia 3. Duration of motor block 4. Hypotension (no supplied study definition) 5. Bradycardia (no supplied study definition) 6. Nausea and vomiting 7. Shivering 8. Pruritus	1. Lower in BD at 1,* 2* hours; ND at 4 hours 2. Longer in BD* 3. Shorter in BD 4. ND 5. Less in BD 6. Less in BD 7. Less in BD 8. ND

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
Mahdy *et al.* 2011[40] Egypt	RCT Low	Sample: 60 Included: • ASA I and II • GA ≥ 36 weeks • BMI not specified • Singleton pregnancies • Age 18-45 years • Elective Excluded: • Cardiac, liver, kidney, neurological disease • Intrauterine growth restriction Additional analgesia: • Not specified	Volume 2.5 mL HB 0.5% 10 mg DEX 5 mcg	Volume 2.5 mL HB 0.5% 10 mg FEN 10 mcg	1. Duration of motor block 2. Hypotension (SBP <100 mmHg and/or >30% decrease from baseline) 3. Bradycardia (HR < 50 bpm) 4. Nausea and vomiting 5. Pruritus	1. Longer in BD* 2. Less in BD 3. Less in BD 4. Less in BD 5. Less in BD*
Mishra *et al.* 2017[43] India	RCT Moderate	Sample: 60 Included: • ASA I and II • GA >36 weeks • BMI not specified • Elective • Age 18-35 years Excluded: • "Same as for regional anesthesia," understood as contraindications to neuraxial anesthesia Additional analgesia: • Not specified	Volume 2.3 mL HB 0.5% 9 mg DEX 5 mcg	Volume 2.3 mL HB 0.5% 9 mg FEN 25 mcg	1. Postoperative pain score 2. Duration of analgesia 3. Duration of motor block 4. Hypotension (no supplied study definition) 5. Bradycardia (no supplied study definition) 6. Nausea and vomiting 7. Pruritus	1. No data provided 2. Longer in BD* 3. Longer in BD* 4. ND 5. ND 6. More in BD 7. Less in BD

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
Mohammed *et al*. 2022[47] Egypt	Prospective observational study Low	Sample: 60 Included: • ASA not specified • GA not specified • BMI not specified • Number of fetuses not specified • Age 18-40 years • Elective surgery Excluded: • Cardiovascular, endocrine, neuromuscular, psychiatric disease Additional analgesia: • Standard analgesia—paracetamol 1 g x 6 hourly (route not specified), pethidine 0.7 mg/kg IM x 6 hourly • Rescue—pethidine 50 mg IM	Volume not specified HB 0.5% 12mg DEX 3mcg	Volume 2.8ml HB 0.5% 12mg FEN 20mcg	1. Postoperative pain score 1, 4, 8, 12 hours 2. Duration of analgesia 3. Duration of motor block 4. Hypotension 5. Nausea and vomiting 6. Shivering 7. Pruritus	1. Less in BD at 1,* 4,* 8, 12* hours 2. No data provided 3. Longer in BD* 4. No data provided 5. No data provided 6. No data provided 7. No data provided
Rajkumar *et al.* 2022[31] India	RCT Moderate	Sample: 66 Included: • ASA I/II • GA not specified • BMI not specified • Number of fetuses not specified • Age 20-35 years • Elective Excluded: • Cardiac, liver, renal, psychiatric disease • Hypertension Additional analgesia: • Not specified	Volume 2.5 mL HB 0.5% 10 mg DEX 5 mcg	Volume 2.5 mL HB 0.5% 10 mg FEN 25 mcg	1. Duration of analgesia 2. Hypotension (no supplied study definition) 3. Bradycardia (no supplied study definition) 4. Nausea and vomiting 5. Pruritus	1. Longer in BD* 2. More in BD 3. More in BD 4. Less in BD 5. ND

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
Rao *et al.* 2019[45] India	RCT Moderate	Sample: 120 Included: • ASA I and II • GA not specified • BMI not specified • Number of fetuses not specified • Age 20-35 years • Urgency of surgery not specified Excluded: • Cardiac, renal, neurological disease • Gestational hypertension • Additional analgesia: • Not specified	Volume 2 mL HB 0.5% 7.5 mg DEX 5 mcg	Volume 2 mL HB 0.5% 7.5 mg FEN 25 mcg	Duration of analgesia	Longer in BD*
Sheikh *et al.* 2021[46] India	Prospective observational study Moderate	Sample: 130 Included: • ASA I and II • GA ≥ 37 weeks • BMI not specified • Elective • Age not specified Excluded: • Valvular heart disease • Placenta previa Additional analgesia: • Standard—not specified • Rescue—tramadol 100 mg IV	Volume 2.5 mL HB 0.5 % 10 mg DEX 10 mcg	Volume 2.5 mL HB 0.5% 10 mg FEN 25 mcg	1. Postoperative pain score at 0, 1, 3, 6 hours 2. Duration of analgesia 3. Duration of motor block 4. Hypotension (SBP <90 mmHg and/or MAP decrease >20% baseline) 5. Bradycardia (HR <50 bpm) 6. Nausea and vomiting 7. Shivering	1. Less in BD at 0,* 1, 3, 6 hours 2. Longer in BD* 3. Shorter in BD 4. Less in BD 5. More in BD 6. Less in BD 7. Less in BD
Sun *et al.* 2015[37] China	RCT Low	Sample: 60 Included: • ASA I and II • GA 36-40 weeks • Singleton pregnancies • BMI not specified • Elective • Age 20-35 years	Volume 3 mL HB 0.5% 10 mg DEX 10 mcg	Volume 3 mL HB 0.5% 10 mg FEN 25 mcg	1. Postoperative pain score at 1, 2, 4 hours 2. Duration of analgesia 3. Duration of motor block 4. Hypotension (SBP <100 mmHg or decrease of >20% from baseline) 5. Bradycardia (HR< 55 bpm) 6. Nausea and vomiting 7. Shivering	1. Lower in BD at 1,* 2, 4 hours 2. Longer in BD* 3. Shorter in BD 4. ND 5. ND 6. Less in BD 7. Less in BD*

(*Continued*)

Study and country	Study design and risk of bias	Participants	Intervention (BD)	Comparator (BF)	Outcomes	Description of main results
		Excluded: • PET • Multiple gestation Additional analgesia: • CSE technique described but no epidural or analgesia via any other route not specified				
Urooj *et al.* 2022[39] Pakistan	RCT Low	Sample: 60 Included: • ASA II and III • Fetus per pregnancy not specified • GA ≥ 35 weeks • BMI < 35 • Elective CS Excluded: • Hypertensive disorders (pregnancy-induced hypertension, PET, eclampsia) Additional analgesia: • Standard—tramadol 50 mg IV x 6 hourly; paracetamol x 8 hourly (route and dose not specified) • Rescue—ketorolac 30 mg (route not specified)	Volume 2.05 mL HB 0.5% 10 mg DEX 5 mcg	Volume 2.20 mL HB 0.5% 10 mg FEN 10 mcg	1. Postoperative pain score at 1, 2, 3, 4 hours 2. Duration of motor block 3. Hypotension (MAP decrease >20% from baseline) 4. Bradycardia (HR <50 bpm) 5. Nausea 6. Vomiting 7. Shivering	1. Lower in BD at 1, 2, 3,* 4* hours 2. Longer in BD* 3. More in BD* 4. Less in BD 5. More in BD* 6. More in BD 7. Less in BD

*Results indicated as statistically significant with $P \leq 0.05$

ASA, American Society of Anesthesiologists; BD, hyperbaric bupivacaine-dexmedetomidine; BF, hyperbaric bupivacaine-fentanyl; BMI, body mass index; bpm, beats per minute; CS, Cesarean section; CSE, combined spinal-epidural; DEX, dexmedetomidine; FEN, fentanyl; GA, gestational age; HB, hyperbaric bupivacaine; HR, heart rate; IM, intramuscular; IV, intravenous; MAP, mean arterial pressure; ND, no difference; PET, preeclampsia; RCT, randomized controlled trial; SBP, systolic blood pressure

Appendix V: Subgroup analyses

Subgroup analyses for duration of analgesia

Subgroup	Number and design of studies	No. of participants	MD, IV, random effects (95% CI)	*P*	Heterogeneity	
					X^2	I^2
Study design						
RCTs	8 RCTs[31,32,36-38,43-45]	576	93.30 minutes more (62.40 to 124.19 minutes more)	0	290.74	98
Non-RCTs	1 non-RCT[46]	130	160.16 minutes more	0	N/A	N/A
Intervention						
Dexmedetomidine ≤5 mcg	6 RCTs[31,32,38,43-45]	476	96.05 minutes more (53.88 to 138.21 minutes more)	0	272.83	99
Dexmedetomidine >5 mcg	2 RCTs[36,37]	102	86 minutes more (75.77 to 96.23 minutes more)	0	0.03	0
Methodological quality						
Low risk of bias	3 RCTs[36-38]	212	107.93 minutes more (63.48 to 152.37 minutes more)	0	24.79	95
Moderate risk of bias	5 RCTs[31,32,43-45]	366	84.53 minutes more (41.26 to 127.80 minutes more)	0	219.4	98

IV, inverse variance; MD, mean difference; N/A, not applicable; RCT, randomized controlled trial

Subgroup analyses for duration of motor block

Subgroup	Number and design of studies	No of participants	MD (minutes), IV, random effects (95% CI)	*P*	Heterogeneity	
					X^2	I^2
Study design						
RCTs	8 RCTs[30,36-41,43]	502	29.68 minutes more (0.96 to 58.40 minutes more)	0	407.86	99
Non-RCTs	2 non-RCTs[46,47]	190	39.38 minutes more (74.67 minutes less to 153.42 minutes more)	0.5	150.1	99
Intervention						
Dexmedetomidine ≤5 mcg	4 RCTs[38-40,43]	290	29.99 minutes more (13.73 minutes less to 73.71 minutes more)	0.18	34.57	95
Dexmedetomidine >5 mcg	4 RCTs[30,36,37,41]	212	39.63 minutes more (8.30 minutes less to 87.56 minutes more)	0.11	149.87	99
Methodological quality						
Low risk of bias	5 RCTs[30,36-38,40]	312	15.90 minutes more (23.50 minutes less to 55.30 minutes more)	0.43	194.9	98
Moderate risk of bias	3 RCTs[39,41,43]	190	67.52 minutes more (61.69 to 73.34 minutes more)	0	0.04	0

IV, inverse variance; MD, mean difference; RCT, randomized controlled trial