Can J Anesth/J Can Anesth (2023) 70:406–442
https://doi.org/10.1007/s12630-022-02389-9

REVIEW ARTICLE/BRIEF REVIEW

Comparison of different delivery modalities of epidural analgesia and intravenous analgesia in labour: a systematic review and network meta-analysis

Comparaison des différentes modalités d'administration de l'analgésie péridurale et de l'analgésie intraveineuse pendant le travail obstétrical : revue systématique et méta-analyse en réseau

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Received: 2 April 2022 / Revised: 15 September 2022 / Accepted: 16 September 2022 / Published online: 31 January 2023

Abstract

Purpose *In labour, neuraxial analgesia is the standard in the provision of pain relief. However, the optimal mode of delivering epidural solution has not been determined, and some parturients may need an alternative to epidural analgesia. We sought to conduct a systematic review and network meta-analysis to compare continuous epidural infusion (CEI), programmed intermittent epidural bolus (PIEB), computer-integrated CEI, computer-integrated PIEB, patient-controlled epidural bolus (PCEA), fentanyl patient-controlled analgesia (PCA), and remifentanil PCA, either alone or in combination.*

Methods *We searched CENTRAL, CINAHL, Ovid Embase, Ovid Medline, and Web of Science for randomized controlled trials that included nulliparous and/or multiparous parturients in spontaneous or induced labour. The maintenance epidural solution had to include a low concentration local anesthetic and an opioid. Specific subgroups in the obstetric population such as preeclampsia were excluded. Network meta-analysis was performed with a frequentist method, and continuous and dichotomous outcomes are presented as mean differences and odds ratios, respectively, with 95% confidence intervals.*

Results *Overall, 73 trials were included. For the first coprimary outcome, the need for rescue analgesia, CEI was inferior to PIEB and PIEB + PCEA was superior to PCEA alone, with a low certainty of evidence given the presence of serious limitations and imprecision. The second coprimary outcome, the maternal satisfaction, was improved by PIEB + PCEA compared with CEI + PCEA and PCEA alone, with a low quality of evidence in view of the presence of serious limitations and imprecision. Fentanyl PCA increased the requirement for rescue analgesia and decreased maternal satisfaction relative to many methods of delivering epidural solution. In terms of secondary outcomes, PIEB increased analgesic efficacy compared with CEI, and PCEA reduced local anesthetic consumption at the expense of inferior analgesia relative to CEI and PIEB. PIEB + PCEA was superior to CEI + PCEA in regard to the pain score at 2 h and 4 h, consumption of local anesthetic, incidence of lower lower limb motor blockade and the rate of spontaneous vaginal delivery. Fentanyl and remifentanil PCA did not provide the same level of analgesia as all epidural methods, resulted in increasing analgesic ineffectiveness with time spent in labour, and predisposed to a higher incidence of side effects such as nausea and/or vomiting and sedation.*

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-022-02389-9.

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Remifentanil PCA was superior to fentanyl PCA for analgesia at an early time point, and it increased the incidence of oxygen desaturation relative to other strategies of delivering epidural solution.

Conclusions *Opioid PCA did not provide the same level of analgesia as epidural methods with a higher incidence of side effects. We interpret the findings of our systematic review and network meta-analysis as suggesting PIEB + PCEA to be the optimal delivery mode of epidural solution. Nevertheless, the potential differing importance of the various maternal, fetal, and neonatal outcomes in determining which is optimal has not, to our knowledge, been elucidated yet.*

Study registration *PROSPERO (CRD42021254978); registered 27 May 2021.*

Résumé

Objectif *Pendant le travail obstétrical, l'analgésie neuraxiale constitue la norme de soins pour soulager la douleur. Néanmoins, le mode optimal d'administration de la solution péridurale n'a pas été déterminé et certaines parturientes pourraient avoir besoin d'une alternative à l'analgésie péridurale. Nous avons cherché à réaliser une revue systématique et une méta-analyse en réseau pour comparer l'analgésie péridurale par perfusion continue (APPC), l'administration programmée de bolus périduraux (PIEB), l'APPC intégrée par ordinateur, l'analgésie péridurale contrôlée par la patiente (l'APCP), l'analgésie contrôlée par la patiente (ACP) de fentanyl et l'ACP de rémifentanil, soit seules ou en combinaison.*

Méthode *Nous avons effectué des recherches dans les bases de données CENTRAL, CINAHL, Ovid Embase, Ovid Medline et Web of Science pour en tirer les études randomisées contrôlées incluant des parturientes nullipares et/ou multipares en travail spontané ou induit. La solution péridurale de maintien devait inclure un anesthésique local à faible concentration et un opioïde. Des sous-groupes spécifiques dans la population obstétricale, comme par exemple les parturientes atteintes de prééclampsie, ont été exclus. Une méta-analyse en réseau a été réalisée à l'aide d'une méthode fréquentiste, et les résultats continus et dichotomiques sont présentés sous forme de différences moyennes et de rapports de cotes, respectivement, avec des intervalles de confiance à 95 %.*

Résultats *Au total, 73 études ont été incluses. Concernant le premier critère d'évaluation coprincipal, soit le besoin d'analgésie de secours, l'APPC était inférieure à la PIEB, et la PIEB + APCP était supérieure à l'APCP seule, avec un faible niveau de fiabilité des données probantes compte tenu de la présence de limitations et d'imprécisions importantes. Le deuxième critère d'évaluation coprincipal, soit la satisfaction maternelle, a été amélioré avec la PIEB + APCP comparativement à l'APPC + APCP et à l'APCP seule, avec une faible qualité de données probantes compte tenu de la présence de limitations et d'imprécisions importantes. L'ACP à base de fentanyl a augmenté le besoin d'analgésie de secours et diminué la satisfaction maternelle par rapport à de nombreuses méthodes d'administration de la solution péridurale. En termes de critères d'évaluation secondaires, la PIEB a amélioré l'efficacité analgésique par rapport à l'APPC, et l'APCP a diminué la consommation d'anesthésiques locaux au détriment d'une analgésie inférieure par rapport à l'APPC et à la PIEB. La PIEB + APCP était supérieure à l'APPC + APCP en ce qui a trait aux scores de douleur à 2 h et 4 h, à la consommation d'anesthésiques locaux, à l'incidence de bloc moteur des membres inférieurs et au taux d'accouchement vaginal spontané. Les ACP de fentanyl et de rémifentanil n'ont pas fourni le même niveau d'analgésie que toutes les méthodes péridurales et ont entraîné une augmentation de l'inefficacité analgésique avec le temps passé en travail actif, en plus de prédisposer les parturientes à une incidence plus élevée d'effets secondaires tels que les nausées et/ou vomissements et la sédation. L'ACP de rémifentanil était supérieure à l'ACP de fentanyl en début d'analgésie mais a augmenté l'incidence de désaturation en oxygène par rapport aux stratégies de livraison de la solution péridurale.*

Conclusion *L'ACP à base d'opioïdes n'a pas fourni le même niveau d'analgésie que les méthodes péridurales, avec une incidence plus élevée d'effets secondaires. Nous interprétons les résultats de notre revue systématique et de notre méta-analyse en réseau comme suggérant que la PIEB + APCP constitue le mode d'administration optimal de la solution péridurale. Néanmoins, la différence potentielle en importance des divers devenirs maternels, fœtaux et néonataux pour déterminer la modalité optimale n'a pas encore été élucidée, à notre connaissance.*

Enregistrement de l'étude *PROSPERO (CRD42021254978); enregistrée le 27 mai 2021.*

Keywords epidural analgesia · labour pain · obstetric labour · patient-controlled analgesia · remifentanil

Labour is one of the most painful experiences that women encounter in their lives,[1] and can be associated with physiologic consequences and long-term emotional and psychological effects.[2,3] Neuraxial analgesia is considered to be the criterion standard in the provision of pain relief in labour.[4,5] But in the face of ongoing research,[6] the optimal mode of delivering epidural solution to produce improved maternal, fetal, and neonatal outcomes has still not been

determined. Continuous epidural infusion (CEI) can be defined as the constant infusion of epidural solution over the course of labour, while intermittent epidural boluses may be administered by many different techniques. They can be given at scheduled time intervals, that is by programmed intermittent epidural bolus (PIEB), or on demand by the clinician as demand intermittent epidural bolus (DIEB) or by the patient as patient-controlled epidural analgesia (PCEA). Computer-integrated CEI and PCEA (CI CEI + PCEA) and computer-integrated PIEB and PCEA (CI PIEB + PCEA) represent more novel delivery systems of epidural solution, in which the rate of infusion of CEI or the frequency of PIEB varies with the pattern of PCEA use through an autoregulatory feedback loop.[7,8]

In some parturients, however, an alternative to epidural analgesia may be needed. Contraindications to neuraxial modalities include allergy to local anesthetics, bleeding diathesis, hemodynamic instability, patient refusal, spinal abnormalities, and suspected infection. In such circumstances, the use of intravenous patient-controlled analgesia (PCA) with opioids is common.[9] It has been suggested that remifentanil, in particular, might be the ideal systemic opioid for pain relief in labour as it has a fast onset of action, short context-sensitive half life, and a rapid offset owing to its metabolism by nonspecific plasma and tissue esterases.[10]

To differentiate between the various strategies of delivering epidural solution, meta-analyses have previously conducted pairwise comparisons to examine CEI *vs* PCEA;[11] CEI + PCEA *vs* PCEA;[12] CEI *vs* PIEB, both with or without PCEA;[13–17] and CEI + PCEA *vs* PIEB + PCEA.[18] The methodology of these systematic reviews was limited by the pooling of disparate interventions such as CEI, CEI + PCEA and CI CEI + PCEA and PIEB, PIEB + PCEA, and CI PIEB + PCEA. Further, meta-analyses have evaluated epidural analgesia *vs* remifentanil PCA,[19–21] but none have looked at the possibility of other opioids such as fentanyl compared with neuraxial analgesia. Given the recent publication of several randomized controlled trials,[6,22–24] a network meta-analysis would facilitate the simultaneous comparison of multiple competing interventions, substituting or supplementing direct comparisons with indirect ones, potentially increasing the precision of effect estimates.

In view of this, the aim of this systematic review and network-meta-analysis was to compare the influence of CEI, CI CEI, CI PIEB, DIEB, fentanyl PCA, PCEA, PIEB, and remifentanil PCA, either alone or in combination with each other, on outcomes related to the mother, fetus, and neonate.

Methods

We prospectively registered the protocol for this systematic review and network meta-analysis with PROSPERO (CRD42021254978), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines when presenting our findings.[25] CENTRAL, CINAHL, Ovid Embase, Ovid Medline, and Web of Science were searched by two authors (D. O. and N. D.) from inception to 6 August 2022 for free-text keywords and subject headings associated with obstetric care, labour, analgesic modalities, and local anesthetics (Electronic Supplementary Material [ESM] eAppendix 1).

Inclusion criteria were met if a randomized controlled trial evaluated nulliparous and/or multiparous patients in spontaneous or induced labour and if they had any of the following analgesic interventions, either alone or in combination with each other: CEI; CI CEI; CI PIEB; DIEB; fentanyl PCA; PCEA; PIEB; and remifentanil PCA. Importantly, PIEB was defined as either the manual or automated scheduled administration of epidural solution, and we did not differentiate between these methods of delivery for PIEB. In the case of neuraxial analgesic techniques, the method of insertion could include epidural, combined spinal-epidural (CSE), or dural puncture epidural. Following the initiation of neuraxial analgesia, the maintenance epidural solution had to include a local anesthetic, at a concentration of bupivacaine or levobupivacaine less than or equal to 0.125% or ropivacaine less than or equal to 0.2%, and an opioid, with no difference in the constituents of this solution between the groups in a trial. Exclusion criteria were satisfied if the randomized controlled trial examined only a specific subgroup in the obstetric population such as preeclampsia, or it was published only as an abstract. We did not place any restrictions on language of publication.

Once the article citations had been deduplicated, two authors (S. W. and N. D.) used the aforementioned inclusion and exclusion criteria to screen their titles and abstracts independently in Rayyan (Qatar Computing Research Institute, 2016, Doha, Qatar).[26] To find trials that had been missed from the database searches, the reference lists of included ones and previous systematic reviews were hand searched.

Characteristics of trials were extracted by two authors (N. D. and D. Z.) for the following: the parity of patients; neuraxial technique if applicable; method of initiation of regional or systemic analgesia; technique of maintenance of regional or systemic analgesia; and the management of breakthrough pain. Quantitative data were extracted by three authors (S. W., D. Z., and B. N.), and disputed differences were settled by a fourth author (N. D.). The

coprimary outcomes were the need for rescue analgesia and the maternal satisfaction. It was our opinion that the efficacy of the different delivery modalities of epidural analgesia and intravenous analgesia from the perspective of pain relief in labour was best reflected by the need for rescue analgesia. Maternal satisfaction was thought to be multidimensional in nature, and have the potential to summarize the subjective influence of these various techniques on indices such as pain, lower limb blockade, duration of labour, mode of delivery, and fetal outcome. Secondary outcomes were related to the mother, fetus, or neonate, and included: the change in baseline pain score; pain score at 30 min, one hour, two hours, three hours, and four hours; overall pain score in labour; time to rescue analgesia; dose of bupivacaine-equivalent local anesthetic per hour; cumulative dose of bupivacaine-equivalent local anesthetic in labour; duration of first stage of labour; duration of second stage of labour; overall duration of labour; incidence of maternal respiratory depression, apnea, oxygen desaturation, bradycardia, sedation, nausea and/or vomiting, pruritus, shivering and lower limb motor blockade; rate of spontaneous vaginal delivery, instrumental delivery, and Cesarean delivery; maternal satisfaction; rate of fetal bradycardia; umbilical pH; and the rate of neonatal Apgar score < 7 at one and five minutes. If we required further information from trial authors, we emailed them up to three times.

We judged the methodological quality of trials with the revised Cochrane risk of bias tool (RoB 2),[27] and two authors (D. O. and A. O.) determined the following risk of biases: randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; and selection of the reported result. Trials were provided with a summary risk of bias which was either low, of some concern, or high, and disputed differences were settled by a third author (N. D.).

Continuous data were extracted as means and standard deviations. In converting the data to these means and standard deviations, we followed recommendations from the Cochrane Collaboration.[28] The mean was presumed to be the same as the median, and the standard deviation was calculated by dividing the interquartile range by 1.35 and the range by 4. Dichotomous data extracted as numbers of incidence. Of note, bupivacaine equivalents were calculated from levobupivacaine and ropivacaine using a factor of 0.6. Outcome data that were presented in graphical but not numerical format were quantified with the use of Plot Digitizer version 2.1 (Free Software Foundation, Boston, MA, USA).

Data were imported from Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) into Stata version 16.1 (StataCorp LLC, College Station, Texas, USA) by two authors (N. D and D. Z.). Network meta-analysis with a common heterogeneity parameter and frequentist and multivariate methods was conducted for an outcome if the direct comparisons between trials of three or more interventions could be linked into a network.[29,30] Empirical and simulation studies suggest no important differences in the performance, bias, or errors between the Bayesian and this frequentist model of network meta-analysis.[31] Network plots were created in which the nodes indicated the interventions and the lines represented the direct comparisons between these interventions. Indirect comparisons, that is those which were not directly compared within trials, were derived mathematically. Local inconsistency between direct and indirect estimates was evaluated by separating indirect evidence from direct evidence, and global inconsistency was examined with the design-by-treatment interaction test. Network league tables were constructed to display the results of multiple comparisons between interventions. Continuous outcome data are presented as mean differences with 95% confidence intervals, and dichotomous outcome data are presented as odds ratios with 95% confidence intervals. In the absence of serious imprecision, competing interventions were ranked in order. The grading of recommendations assessment, development, and evaluation (GRADE) system for network meta-analysis, as recommended by Salanti *et al.*,[32] was used by two authors (D. Z. and N. D.) to evaluate the certainty and quality of evidence for all outcomes, and the following domains were studied: risk of bias; indirectness; imprecision; inconsistency; and publication bias. This was supported by the use of CINeMA software (Institute of Social and Preventative Medicine, University of Bern, Bern, Switzerland), and the use of a comparison-adjusted funnel plot and the Egger's linear regression test.

Results

In all, 73 trials were included in the systematic review,[6–8,22–24,33–99] and details of the screening process are illustrated in Fig. 1. The following interventions were compared: CEI *vs* DIEB in two trials;[33,34] CEI *vs* PIEB in ten trials;[35–42,96,97] CEI *vs* PCEA in eight trials;[43–50] CEI *vs* DIEB *vs* PCEA in two trials;[51,52] CEI *vs* CEI + PCEA in four trials;[53–55,99] CEI *vs* CI CEI + PCEA in one trial;[7] CEI *vs* CEI + PCEA *vs* PCEA in three trials;[56–58] CEI + DIEB *vs* DIEB in one trial;[59] CEI *vs* remifentanil PCA in four trials;[60–63] CEI + PCEA *vs* DIEB in one trial;[64] CEI + PCEA *vs* PCEA in ten trials;[65–74] CEI + PCEA *vs* PIEB + DIEB in one trial;[75] CEI + PCEA *vs* PIEB + PCEA in ten trials;[6,22,23,76–82] CEI + PCEA *vs* CI PIEB + PCEA in three trials;[8,83,84] CEI + PCEA *vs* CEI + PIEB + PCEA in two trials;[85,86] CEI + PCEA *vs* remifentanil PCA in one

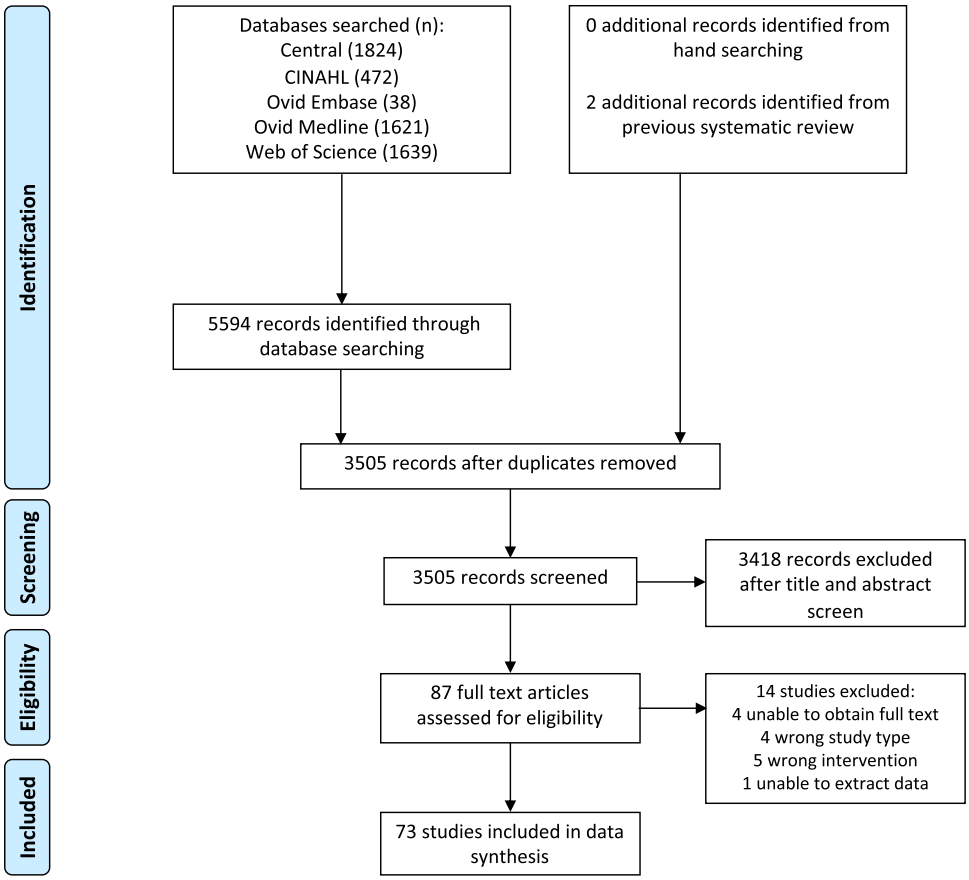

Fig. 1 PRISMA flow diagram summarizing the retrieved, included, and excluded randomized controlled trials. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

trial;[87] CI CEI + PCEA *vs* PCEA in one trial;[88] CI CEI + PCEA *vs* CEI + PCEA in one trial;[89] DIEB *vs* PCEA in three trials;[90–92] PIEB *vs* remifentanil PCA in one tria;l[93] PIEB + PCEA *vs* PCEA in two trials;[24,98] PCEA *vs* fentanyl PCA in one trial;[94] and fentanyl PCA *vs* remifentanil PCA in one trial.[95] The findings of the risk of bias assessment are presented in Fig. 2, and none of the trials were evaluated as having an overall low risk. Some concerns were present in regard to the risk of bias in 43 trials[6–8,22,24,33–36,38–41,44,48,50–52,55,57,59,61,62,64–66,68–70,77,78,83–89,91,94–96,98] and the risk of bias was high in 30 trials.[23,37,42,43,45–47,49,53,54,56,58,60,63,67,71–76,79–82,90,92,93,97,99] To clarify the methodology and results of the trials, 33 authors were emailed and four responded with the requested information.[49,71,72,82]

Characteristics of the trials are detailed in Table 1. Participants were nulliparous in 41 trials,[6,8,24,33–39,44,46,49,50,52,54,55,58,59,61,69,70,72,77–86,88,89,92–94,96,98,99] multiparous in one trial,[76] nulliparous and multiparous in 28 trials,[22,23,40–43,47,48,51,53,56,57,60,62–68,71,73–75,87,90,91,95] and not specified in three trials.[7,45,97] Epidural, performed in 53 trials,[22,23,33,34,37,39–51,53–57,60,62–67,71–75,77–82,85–87,90–94,96–99] was the main neuraxial technique. CSE was used in 16 trials,[7,8,24,35,36,38,52,58,68–70,76,83,84,88,89] epidural or dural puncture epidural in one trial,[6] and epidural or CSE in two trials.[59,61] In the epidural analgesic solution, the local anesthetic was bupivacaine in 24 trials,[22,39,41–45,49,51–53,56,58,59,64,65,71,76,87,90–94] levobupivacaine in 13 trials,[34,36,48,50,61,72,73,77,82,85,86,97,98] ropivacaine in 33 trials,[6–8,23,24,35,37,38,40,46,47,54,57,60,62,63,66–70,74,75,78–81,83,84,88,89,96,99], and bupivacaine or ropivacaine in two trials.[33,55] The opioid was fentanyl in 55 trials[7,8,22,23,33–46,48–50,52–59,61,62,64,65,69–74,76,79,83–90,92–94,96,97,99] and sufentanil in 17 trials.[6,24,47,51,60,63,66–68,75,77,78,80–82,91,98]

Our first coprimary outcome, the need for rescue analgesia, was examined in 3,963 participants and 40 trials.[6–8,22–24,36–42,47–51,57,58,65,66,68,71–73,76,77,82–84,87,89,91,92,94–98] The trials differed in their definition of the outcome and these definitions included: additional analgesia requested by the patient; inadequate analgesia; pain score greater than two, three, four or five out of ten; and not specified. In the network plot, 13 direct comparisons and 32 indirect comparisons were established between ten interventions (Fig. 3). Continuous epidural infusion was

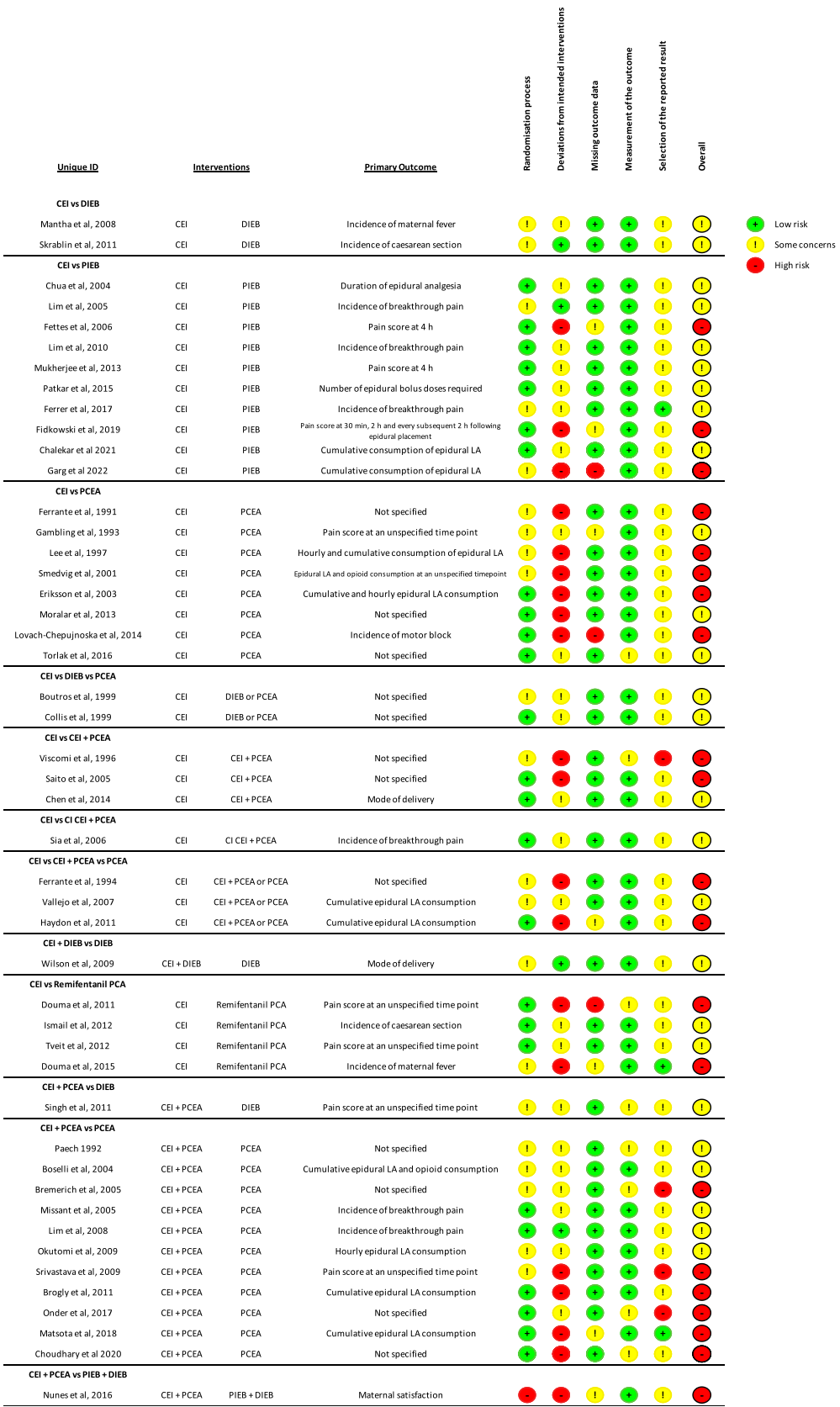

Fig. 2 Risk of bias assessment of included trials using the revised Cochrane tool. ?, some concerns; !, some concerns; -, high risk; +, low risk

CEI + PCEA vs PIEB + PCEA								
Wong et al, 2006	CEI + PCEA	PIEB + PCEA	Hourly epidural LA consumption	+	-	+	+	!	-
Capogna et al, 2011	CEI + PCEA	PIEB + PCEA	Incidence of motor block	!	!	+	+	!	!
Feng et al, 2014	CEI + PCEA	PIEB + PCEA	Incidence of maternal fever	+	!	+	+	+	!
Lin et al, 2015	CEI + PCEA	PIEB + PCEA	Not specified	+	-	+	+	!	-
Lin et al, 2016	CEI + PCEA	PIEB + PCEA	Not specified	+	!	+	+	!	-
Fan et al, 2019	CEI + PCEA	PIEB + PCEA	Not specified	+	-	+	+	+	-
Morau et al, 2019	CEI + PCEA	PIEB + PCEA	Composite endpoint of objective labour events	!	-	+	+	!	-
Haidl et al, 2020	CEI + PCEA	PIEB + PCEA	Hourly epidural LA consumption	+	!	+	+	+	!
Ojo et al, 2020	CEI + PCEA	PIEB + PCEA	Hourly epidural LA consumption	+	-	+	+	+	-
Song et al, 2021	CEI + PCEA	PIEB + PCEA	Time to specified decrease in pain score	!	!	+	+	+	!
CEI + PCEA vs CI PIEB + PCEA								
Sia et al, 2007	CEI + PCEA	CI PIEB + PCEA	Hourly epidural LA consumption	+	!	+	+	!	!
Leo et al, 2010	CEI + PCEA	CI PIEB + PCEA	Incidence of breakthrough pain	+	!	+	+	!	!
Sia et al, 2013	CEI + PCEA	CI PIEB + PCEA	Incidence of breakthrough pain	+	+	+	+	!	!
CEI + PCEA vs CEI + PIEB + PCEA								
Diez-Picazo et al, 2019	CEI + PCEA	CEI + PIEB + PCEA	Incidence of breakthrough pain	!	!	+	+	+	!
Rodriguez-Campoo et al, 2019	CEI + PCEA	CEI + PIEB + PCEA	Cumulative epidural LA consumption	+	!	+	+	!	!
CEI + PCEA vs Remifentanil PCA								
Stocki et al, 2014	CEI + PCEA	Remifentanil PCA	Pain score every h	+	!	+	!	+	!
CI CEI + PCEA vs PCEA								
Lim et al, 2006	CI CEI + PCEA	PCEA	Hourly epidural LA consumption	+	!	+	+	!	!
CI CEI + PCEA vs CEI + PCEA								
Sng et al, 2009	CI CEI + PCEA	CEI + PCEA	Hourly epidural LA consumption	+	!	+	+	!	!
DIEB vs PCEA								
Paech et al, 1995	DIEB	PCEA	Not specified	!	-	!	!	!	-
Vandermeulen et al, 1995	DIEB	PCEA	Not specified	!	!	+	!	!	!
Nikkola et al, 2006	DIEB	PCEA	Not specified	!	-	!	!	!	-
PIEB vs Remifentanil PCA								
Karadjova et al, 2019	PIEB	Remifentanil PCA	Not specified	-	!	+	+	!	-
PIEB + PCEA vs PCEA								
Roofthooft et al, 2020	PIEB + PCEA	PCEA	Incidence of breakthrough pain	+	!	+	+	+	!
Bourges et al 2021	PIEB + PCEA	PCEA	Hourly epidural LA consumption	+	+	!	+	+	!
PCEA vs Fentanyl PCA								
Halpern et al, 2004	PCEA	Fentanyl PCA	Incidence of caesarean section	+	+	+	+	!	!
Fentanyl PCA vs Remifentanil PCA								
Douma et al, 2010	Fentanyl PCA	Remifentanil PCA	Pain score every h	+	!	+	+	!	!

CEI, continuous epidural infusion; CI, computer integrated; DIEB, demand intermittent epidural bolus; LA, local anaesthetic; PCA, patient controlled analgesia; PCEA, patient controlled epidural analgesia; PIEB, intermittent epidural bolus.

inferior to PIEB and PIEB + PCEA, and PIEB + PCEA was superior to PCEA. Fentanyl PCA was inferior to CEI + PCEA, CI CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA (Table 2). Inconsistency was present between three comparisons, namely PCEA *vs* fentanyl PCA, CEI + PCEA *vs* remifentanil PCA, and fentanyl PCA *vs* remifentanil PCA. Overall inconsistency in the network was not revealed. Further, the standard deviation of the between-trials heterogeneity was 0.789. Publication bias was not uncovered on examination of the comparison-adjusted network plot and with the Egger's test ($P = 0.81$) (Fig. 4). The quality of evidence was graded as low (ESM eAppendix 2), and the network ranking of interventions was not performed given the serious imprecision.[100]

Our second coprimary outcome, the maternal satisfaction, was examined in 5,779 participants and 29 trials.[6–8,24,36,38,51,52,57,60,62,63,66,69,72,73,75,76,81–84,87–89,92–95] The trials varied in their definition of the outcome and these definitions included: satisfaction with labour analgesia; neuraxial analgesia or technique; and not specified. Further, maternal satisfaction was assessed on a scale out of five, ten, or 100 and recorded during labour, at an unspecified time point after delivery, within two hours or 24 hr of delivery, at 24 hr or the day following delivery, or prior to discharge from the delivery suite. In the network plot, 18 direct comparisons and 37 indirect comparisons were established between 11 interventions (Fig. 5). Programmed intermittent epidural bolus + PCEA was superior to CEI + PCEA and PCEA, and fentanyl PCA was inferior to CI CEI + PCEA, CI PIEB + PCEA, PIEB, PIEB + PCEA, and remifentanil PCA (Table 2). Inconsistency was present between one comparison, specifically CEI *vs* DIEB, and overall inconsistency in the network was not revealed. Moreover, the standard deviation of the between-trials heterogeneity was 0.589.

Table 1 Characteristics of the included trials

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
CEI vs DIEB				***CEI***		***DIEB***		
Mantha et al., 2008[33]	CEI (N = 46) DIEB (N = 46)	Nulliparous	Epidural	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 8 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ or 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ as well as 100 µg fentanyl	Continuous infusion of 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ or 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10–15 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 8 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ or 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ as well as 100 µg fentanyl	When required, boluses of 10–15 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ or 0.1% ropivacaine with fentanyl 2 $\mu g.mL^{-1}$	Not specified
Skrablin et al., 2011[34]	CEI (N = 104) DIEB (N = 101)	Nulliparous	Epidural	Initial bolus of 20 mL 0.07% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ followed by the same bolus 15 min later if needed	Continuous infusion of levobupivacaine of unspecified concentration with fentanyl 2.5 $\mu g \cdot mL^{-1}$ at a rate of up to 14 $mL \cdot hr^{-1}$	Initial bolus of 20 mL 0.07% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ followed by the same bolus 15 min later if needed	When required, boluses of 20 mL levobupivacaine of unspecified concentration with fentanyl 2.5 $\mu g \cdot mL^{-1}$	Not specified
CEI *vs* PIEB				***CEI***		***PIEB***		
Chua et al., 2004[35]	CEI (N = 21) PIEB (N = 21)	Nulliparous	CSE	Intrathecal bolus of fentanyl 25 µg Epidural test dose of 3 mL 1.5% lidocaine	Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$	Intrathecal bolus of fentanyl 25 µg Epidural test dose of 3 mL 1.5% lidocaine	Regular boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g.mL^{-1}$ every hour	Boluses of 5 mL 0.2% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and subsequent continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$
Lim et al., 2005[36]	CEI (N = 30) PIEB (N = 30)	Nulliparous	CSE	Intrathecal bolus of fentanyl 25 µg Epidural test dose of 3 mL 1.5% lidocaine	Continuous infusion of 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Intrathecal bolus of fentanyl 25 µg Epidural test dose of 3 mL 1.5% lidocaine	Regular boluses of 5 mL 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every 30 min	Boluses of 5 mL 0.2% levobupivacaine
Fettes et al., 2006[37]	CEI (N = 20) PIEB (N = 20)	Nulliparous	Epidural	Epidural test dose of 5 mL 0.2% ropivacaine followed by 10–15 mL 0.2% ropivacaine	Continuous infusion of 0.2% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Epidural test dose of 5 mL 0.2% ropivacaine followed by 10–15 mL 0.2% ropivacaine	Regular boluses of 10 mL 0.2% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 10 mL 0.2% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Lim et al., 2010[38]	CEI (N = 25) PIEB (N = 25)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 3 mL 1.5% lidocaine	Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 3 mL 1.5% lidocaine	Regular boluses of 2.5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every 15 min	Boluses of 5 mL 0.2% ropivacaine
Mukherjee et al., 2013[39]	CEI (N = 30) PIEB (N = 30)	Nulliparous	Epidural	Epidural test dose of 5 mL 0.125% bupivacaine followed by 10 mL 0.125% bupivacaine	Continuous infusion of 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Epidural test dose of 5 mL 0.125% bupivacaine followed by 10 mL 0.125% bupivacaine	Regular boluses of 10 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 10 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Patkar et al., 2015[40]	CEI (N = 30) PIEB (N = 30)	Nulliparous and multiparous	Epidural	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by boluses of 0.2% ropivacaine till adequate pain relief or sensory blockade to T10	Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by boluses of 0.2% ropivacaine till adequate pain relief or sensory blockade to T10	Regular boluses of 10 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 3–5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Ferrer et al·, 2017[41]	CEI (N = 64) PIEB (N = 64)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.1% bupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Initial bolus of 10 mL 0.1% bupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$	Regular boluses of 10 mL 0·1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Fidkowski et al., 2019[42]	CEI (N = 34) PIEB (N = 84)	Nulliparous and multiparous	Epidural	Epidural test dose of 3–5 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 5 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Epidural test dose of 3–5 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 5 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Regular boluses of 5 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every 30 min or 10 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Discretion of the anesthesiologist
Chalekar et al, 2021[96]	CEI (N = 30) PIEB (N = 30)	Nulliparous	Epidural	Epidural test dose of 3 mL 2% lidocaine with adrenaline of unspecified concentration followed by 12 mL 0.15% ropivacaine with 50 µg fentanyl Subsequent bolus of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ if needed for sensory blockade to T10	Continuous infusion of 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 2% lidocaine with adrenaline of unspecified concentration followed by 12 mL 0.15% ropivacaine with 50 µg fentanyl Subsequent bolus of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ if needed for sensory blockade to T10	Regular boluses of 8 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 8 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Garg et al, 2022[97]	CEI (N = 40) PIEB (N = 40)	Not specified	Epidural	Initial bolus of 10 mL 0.1% levobupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$	Continuous epidural infusion of 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	Initial bolus of 10 mL 0.1% levobupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$	Regular boluses of 8 mL 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	Boluses of 8 mL 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
CEI vs PCEA				***CEI***		***PCEA***		
Ferrante et al., 1991[43]	CEI (N = 20) PCEA (N = 20)	Nulliparous and multiparous	Epidural	Initial bolus of 8–13 mL 0.5% bupivacaine	Continuous infusion of 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 12 $mL \cdot hr^{-1}$	Initial bolus of 8–13 mL 0.5% bupivacaine	Patient-controlled boluses of 3 mL 0.125% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 3 mL 0.25% bupivacaine
Gambling et al., 1993[44]	CEI (N = 13) PCEA (N = 55)	Nulliparous	Epidural	Initial bolus of 8–10 mL 0.25% bupivacaine	Continuous infusion of 0.125% bupivacaine with adrenaline 2.5 $\mu g \cdot mL^{-1}$ and fentanyl 2.5 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	Initial bolus of 8–10 mL 0.25% bupivacaine	Patient-controlled boluses of 2, 3, 4 or 6 mL 0.125% bupivacaine with adrenaline 2.5 $\mu g \cdot mL^{-1}$ and fentanyl 2.5 $\mu g \cdot mL^{-1}$ and lockout interval of 10, 15, 20, or 30 min, respectively	Boluses of 0.125–0.5% bupivacaine of unspecified volume or 25–100 µg fentanyl If required, 12 mL 0.125% bupivacaine with adrenaline 1.25 $\mu g \cdot mL^{-1}$

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Lee et al., 1997[45]	CEI (N = 20) PCEA (N = 20)	Not specified	Epidural	Epidural test dose of 5 mL 2% lidocaine followed by 12 mL 0.25% bupivacaine with fentanyl 8 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 12 $mL \cdot hr^{-1}$	Epidural test dose of 5 mL 2% lidocaine followed by 12 mL 0.25% bupivacaine with fentanyl 8 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 4 mL 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Boluses of 0.0625% bupivacaine of unspecified volume
Smedvig et al., 2001[46]	CEI (N = 30) PCEA (N = 29)	Nulliparous	Epidural	Initial bolus of 15 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	Initial bolus of 15 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Eriksson et al., 2003[47]	CEI (N = 40) PCEA (N = 40)	Nulliparous and multiparous	Epidural	Epidural test dose of 3 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ followed by 5 mL of the same solution	Continuous infusion of 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 6–12 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ followed by 5 mL of the same solution	Patient-controlled boluses of 4 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Boluses of 5 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$
Moralar et al., 2013[48]	CEI (N = 22) PCEA (N = 23)	Nulliparous and multiparous	Epidural	Epidural test dose of 2.5 mL 2% lidocaine followed by 10–15 mL 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.0625% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	Epidural test dose of 2.5 mL 2% lidocaine followed by 10–15 mL 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 4 mL 0.0625% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Not specified
Lovach-Chepujnoska et al., 2014[49]	CEI (N = 27) PCEA (N = 24)	Nulliparous	Epidural	Epidural test dose of 3 mL 1.5% lidocaine followed by 10–13 mL 0.08% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.08–0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 1.5% lidocaine followed by 10–13 mL 0.08% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 5 mL 0.08–0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Boluses of 5 mL 0.08–0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Torlak et al., 2016[50]	CEI (N = 20) PCEA (N = 20)	Nulliparous	Epidural	Epidural test dose of 3 mL 2% lidocaine followed by 10 mL 0.125% levobupivacaine with 100 μg fentanyl	Continuous infusion of 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 12 $mL \cdot hr^{-1}$	Epidural test dose of 3 mL 2% lidocaine followed by 10 mL 0.125% levobupivacaine with 100 μg fentanyl	Patient-controlled boluses of 4 mL 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Boluses of 4 mL 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
CEI vs DIEB vs PCEA				***CEI***		***DIEB or PCEA***		
Boutros et al., 1999[51]	CEI (N = 50) DIEB (N = 48) PCEA (N = 48)	Nulliparous and multiparous	Epidural	Initial boluses of 3 mL 0.25% bupivacaine with 10 μg sufentanil till adequate pain relief	Continuous infusion of 0.125% bupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 8–14 $mL \cdot hr^{-1}$	Initial boluses of 3 mL 0.25% bupivacaine with 10 μg sufentanil till adequate pain relief	DIEB: When required, boluses of 5 mL 0.125% bupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.125% bupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5–20 mL 0.125% bupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Collis et al., 1999[52]	CEI (N = 46) DIEB (N = 43) PCEA (N = 44)	Nulliparous	CSE	Intrathecal bolus of 1 mL 0.25% bupivacaine and fentanyl 25 μg	Continuous infusion of 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Intrathecal bolus of 1 mL 0.25% bupivacaine and fentanyl 25 μg	DIEB: When required, boluses of 10 mL 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} PCEA: Patient-controlled boluses of 10 mL 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 30 min	Boluses of 10–15 mL 0.1% bupivacaine with fentanyl 2 μg·mL^{-1}
CEI vs CEI + PCEA				***CEI***		***CEI + PCEA***		
Viscomi et al., 1991[53]	CEI (N = 28) CEI + PCEA (N = 47)	Nulliparous and multiparous	Epidural	Epidural test dose of 2 mL 2% lidocaine followed by 5 mL 2% lidocaine Subsequent bolus of 5 mL 0.25% bupivacaine if needed for adequate pain relief or sensory blockade to T10	Continuous infusion of 0.125% bupivacaine with fentanyl 1 μg·mL^{-1} at a rate of 12 mL·hr^{-1}, adjusted in increments of 2 mL·hr^{-1} to attain sensory blockade to T10	Epidural test dose of 2 mL 2% lidocaine followed by 5 mL 2% lidocaine Subsequent bolus of 5 mL 0.25% bupivacaine if needed for adequate pain relief or sensory blockade to T10	CEI: Continuous infusion of 0.125% bupivacaine with fentanyl 1 μg·mL^{-1} at a rate of 4 mL·hr^{-1} PCEA: Patient-controlled boluses of 4 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Boluses of 10 mL 0.25% bupivacaine
Saito et al., 2005[54]	CEI (N = 29) CEI + PCEA (N = 29)	Nulliparous	Epidural	Epidural test dose of 3 mL 0.2% ropivacaine followed by 8 mL 0.2% ropivacaine	Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Epidural test dose of 3 mL 0.2% ropivacaine followed by 8 mL 0.2% ropivacaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 6 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	CEI: Boluses of 8 mL 0.2% ropivacaine
Chen et al., 2014[55]	CEI (N = 240) CEI + PCEA (N = 240)	Nulliparous	Epidural	Epidural test dose of 5 mL 1% lidocaine with adrenaline of unspecified concentration followed by 10–15 mL 0.08% bupivacaine or 0.1% ropivacaine with fentanyl 2 μg·mL^{-1}	Continuous infusion of 0.08% bupivacaine or 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Epidural test dose of 5 mL 1% lidocaine with adrenaline of unspecified concentration followed by 10–15 mL 0.08% bupivacaine or 0.1% ropivacaine with fentanyl 2 μg·mL^{-1}	CEI: Continuous infusion of 0.08% bupivacaine or 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.08% bupivacaine or 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and unspecified lockout interval	Not specified
CEI vs CI CEI + PCEA				***CEI***		***CI CEI + PCEA***		

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Sia et al., 2006[7]	CEI (N = 20) CI CEI + PCEA (N = 20)	Not specified	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Initial epidural bolus of 2 mL 1.5% lidocaine	Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Initial epidural bolus of 2 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min Depending on frequency of patient-controlled boluses, computer-integrated continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 0–15 mL·hr^{-1}	Boluses of 5 mL 0.2% ropivacaine followed by fentanyl 50 μg
CEI vs CEI + PCEA vs PCEA				***CEI***		***CEI + PCEA or PCEA***		
Ferrante et al., 1994[56]	CEI (N = 15) CEI + PCEA (N = 30) PCEA (N = 15)	Nulliparous and multiparous	Epidural	Initial bolus of 0.5% bupivacaine of variable volume till sensory blockade to T10	Continuous infusion of 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 12 mL·hr^{-1}	Initial bolus of 0.5% bupivacaine of variable volume till sensory blockade to T10	CEI: Continuous infusion of 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 3 or 6 mL·hr^{-1} PCEA: Patient-controlled boluses of 3 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Boluses of 3 mL 0.25% bupivacaine
Vallejo et al., 2007[57]	CEI (N = 62) CEI + PCEA (N = 64) PCEA (N = 63)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.1% ropivacaine with 100 μg fentanyl	Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Initial bolus of 10 mL 0.1% ropivacaine with 100 μg fentanyl	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 15–20 min	Boluses of 10 –20 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and, if required, 5 mL 1.5% lidocaine
Haydon et al., 2011[58]	CEI (N = 83) CEI + PCEA (N = 87) PCEA (N = 84)	Nulliparous	CSE	Intrathecal bolus of 0.4 mL 0.5% bupivacaine and fentanyl 20 μg	Continuous infusion of 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1}	Intrathecal bolus of 0.4 mL 0.5% bupivacaine and fentanyl 20 μg	CEI: Continuous infusion of 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1} PCEA: Patient-controlled boluses of 10 mL 0.1% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 20 min	Boluses of 10 mL 0.25% bupivacaine
CEI + DIEB vs DIEB				***CEI + DIEB***		***DIEB***		

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Wilson et al., 2009[59]	CEI + DIEB (N = 350) DIEB (N = 351)	Nulliparous	Epidural or CSE	Initial bolus of 15 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$ DIEB: When required, boluses of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Intrathecal bolus of 1 mL 0.25% bupivacaine and fentanyl 25 µg Epidural bolus of 15 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	When required, boluses of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Bolus of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and, if required, 5–10 mL 0.25% bupivacaine
CEI vs remifentanil PCA				***CEI***		***Remifentanil PCA***		
Douma et al., 2011[60]	CEI (N = 10) Remifentanil PCA (N = 10)	Nulliparous and multiparous	Epidural in CEI only	Initial bolus of 12.5 mL 0.2% ropivacaine	Continuous infusion of 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	Initial bolus of 40 µg	Patient-controlled boluses of 40 µg and lockout interval of 2 min	CEI: Boluses of 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ of unspecified volume
Ismail et al., 2012[61]	CEI (N = 760) Remifentanil PCA (N = 380)	Nulliparous	Epidural or CSE in CEI only	CSE only: Intrathecal bolus of levobupivacaine 2 mg and fentanyl 15 µg Epidural and CSE: Epidural test dose of 3 mL 2% lidocaine followed by 8 mL 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.125% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$	-	Patient-controlled boluses of 0.1–0.9 $\mu g \cdot kg^{-1}$ and lockout interval of 1 min	CEI: Boluses of 5–10 mL 0.125% levobupivacaine
Tveit et al., 2012[62]	CEI (N = 20) Remifentanil PCA (N = 17)	Nulliparous and multiparous	Epidural in CEI only	Initial bolus of 15 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5–15 $mL \cdot hr^{-1}$	-	Patient-controlled boluses of 0.15 $\mu g \cdot kg^{-1}$, adjusted if required in increments of 0.15 $\mu g \cdot kg^{-1}$, and lockout interval of 2 min	CEI: Boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Douma et al., 2015[63]	CEI (N = 49) Remifentanil PCA (N = 49)	Nulliparous and multiparous	Epidural in CEI only	Initial bolus of 12.5 mL 0.2% ropivacaine	Continuous infusion of 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$	-	Patient-controlled boluses of 40 µg and lockout interval of 2 min	CEI: Boluses of 10 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$
CEI + PCEA vs DIEB				***CEI + PCEA***		***DIEB***		
Singh et al., 2011[64]	CEI + PCEA (N = 30) DIEB (N = 30)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.1% bupivacaine with fentanyl 50 µg	CEI: Continuous infusion of 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 6 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 3 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Initial bolus of 10 mL 0.1% bupivacaine with fentanyl 50 µg	When required, boluses of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Not specified

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
CEI + PCEA vs PCEA				***CEI + PCEA***		***PCEA***		
Paech 1992[65]	CEI + PCEA (N = 25) PCEA (N = 25)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$ followed by 4 mL 0.5% bupivacaine if needed	CEI: Continuous infusion of 0.125% bupivacaine with fentanyl 3 $\mu g \cdot mL^{-1}$ at a rate of 4 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 4 mL 0.125% bupivacaine with fentanyl 3 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$ followed by 4 mL 0.5% bupivacaine if needed	Patient-controlled boluses of 4 mL 0.125% bupivacaine with fentanyl 5 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Boluses of 4 mL 0.5% bupivacaine
Boselli et al., 2004[66]	CEI + PCEA (N = 99) PCEA (N = 34)	Nulliparous and multiparous	Epidural	Initial bolus of 12 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 3–9 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 5 min	Initial bolus of 12 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 5 min	Boluses of 5 mL 0.1% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$
Bremerich et al., 2005[67]	CEI + PCEA (N = 33) PCEA (N = 33)	Nulliparous and multiparous	Epidural	Epidural test dose of ropivacaine 10 mg followed by ropivacaine 16 mg with sufentanil 10 μg	CEI: Continuous infusion of 0.16% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 4 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 4 mL 0.16% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Epidural test dose of ropivacaine 10 mg followed by ropivacaine 16 mg with sufentanil 10 μg	Patient-controlled boluses of 4 mL 0.16% ropivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Not specified
Missant et al., 2005[68]	CEI + PCEA (N = 40) PCEA (N = 38)	Nulliparous and multiparous	CSE	Intrathecal bolus of ropivacaine 3 mg and sufentanil 1.5 μg	CEI: Continuous infusion of 0.15% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ at a rate of 2 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 4 mL 0.15% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Intrathecal bolus of ropivacaine 3 mg and sufentanil 1.5 μg	Patient-controlled boluses of 4 mL 0.15% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Boluses of 10 mL 0.15% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Lim et al., 2008[69]	CEI + PCEA (N = 200) PCEA (N = 100)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 5–10 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10–12 min	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 15 min	Boluses of 5 mL 0.2% ropivacaine
Okutomi et al., 2009[70]	CEI + PCEA (N = 33) PCEA (N = 33)	Nulliparous	CSE	Intrathecal bolus of bupivacaine 2.5 mg and fentanyl 25 μg	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 6 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Intrathecal bolus of bupivacaine 2.5 mg and fentanyl 25 μg	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Not specified
Srivastava et al., 2009[71]	CEI + PCEA (N = 25) PCEA (N = 30)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1}	CEI: Continuous infusion of 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} at a rate of 10 mL·hr^{-1} PCEA: Patient-controlled boluses of 3 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1}	Patient-controlled boluses of 8 mL 0.125% bupivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 20 min	Boluses of 5–10 mL 0.125% bupivacaine
Brogly et al., 2011[72]	CEI + PCEA (N = 20) PCEA (N = 17)	Nulliparous	Epidural	Initial bolus of 10 mL 0.125% levobupivacaine with fentanyl 1.5 μg·mL^{-1}	CEI: Continuous infusion of 0.125% levobupivacaine with fentanyl 1.5 μg·mL^{-1} at a rate of 10 mL·hr^{-1} PCEA: Patient-controlled boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.5 μg·mL^{-1} and lockout interval of 20 min	Initial bolus of 10 mL 0.125% levobupivacaine with fentanyl 1.5 μg·mL^{-1}	Patient-controlled boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.5 μg·mL^{-1} and lockout interval of 20 min	Boluses of 6–8 mL 0.2% ropivacaine

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Onder et al., 2017[73]	CEI + PCEA (N = 25) PCEA (N = 25)	Nulliparous and multiparous	Epidural	Epidural test dose of 2 mL 2% lidocaine followed by 5 mL 2% lidocaine	CEI: Continuous infusion of 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 6 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 6 mL 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Epidural test dose of 2 mL 2% lidocaine followed by 5 mL 2% lidocaine	Patient-controlled boluses of 6 mL 0.1% levobupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Not specified
Matsota et al., 2018[74]	CEI + PCEA (N = 26) PCEA (N = 26)	Nulliparous and multiparous	Epidural	Epidural test dose of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Epidural test dose of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5 mL 0.15% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$
Choudhary 2020[99]	CEI (N = 38) CEI + PCEA (N = 38)	Nulliparous	Epidural	Epidural test dose of 3 mL 2% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 8–10 mL bolus of unspecified constituents	CEI: Continuous infusion of 0.125% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.125% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 mins	Epidural test dose of 3 mL 2% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 8–10 mL bolus of unspecified constituents	Patient-controlled boluses of 5 mL 0.125% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 mins	Not specified
CEI + PCEA vs PIEB + DIEB				***CEI + PCEA***		***PIEB + DIEB***		
Nunes et al., 2016[75]	CEI + PCEA (N = 60) PIEB + DIEB (N = 70)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.16% ropivacaine with sufentanil 10 µg	CEI: Continuous infusion of 0.15% ropivacaine with sufentanil 0.2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.15% ropivacaine with sufentanil 0.2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Initial bolus of 10 mL 0.16% ropivacaine with sufentanil 10 µg	PIEB: Regular boluses of 10 mL 0.1–0.15% ropivacaine with sufentanil 0.2 $\mu g \cdot mL^{-1}$ every hour DIEB: When required, boluses of 5 mL 0.1–0.15% ropivacaine with sufentanil 0.2 $\mu g \cdot mL^{-1}$	PCEA for CEI + PCEA and DIEB for PIEB + DIEB

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
CEI + PCEA vs PIEB + PCEA				***CEI + PCEA***		***PIEB + PCEA***		
Wong et al., 2006[76]	CEI + PCEA (*N* = 63) PIEB + PCEA (*N* = 63)	Multiparous	CSE	Intrathecal bolus of bupivacaine 1.25 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 12 $mL \cdot hr^{-1}$ PCEA: Patient- controlled boluses of 5 mL 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Intrathecal bolus of bupivacaine 1.25 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$	PIEB: Regular boluses of 6 mL 0·0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every 30 min PCEA: Patient-controlled boluses of 5 mL 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5–15 mL 0.125% bupivacaine
Capogna et al., 2011[77]	CEI + PCEA (*N* = 70) PIEB + PCEA (*N* = 75)	Nulliparous	Epidural	Initial bolus of 20 mL 0.0625% levobupivacaine with sufentanil 10 μg	CEI: Continuous infusion of 0.0625% levobupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.125% levobupivacaine and lockout interval of 10 min	Initial bolus of 20 mL 0.0625% levobupivacaine with sufentanil 10 μg	PIEB: Regular boluses of 10 mL 0.0625% levobupivacaine with sufentanil 0.5 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.125% levobupivacaine and lockout interval of 10 min	Boluses of 5 mL 0.125% levobupivacaine
Feng et al., 2014[78]	CEI + PCEA (*N* = 62) PIEB + PCEA (*N* = 63)	Nulliparous	Epidural	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.125% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ and lockout interval of 30 min	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.125% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$	PIEB: Regular boluses of 10 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ and lockout interval of 30 min	Boluses of 5–10 mL 0.15% ropivacaine
Lin et al., 2015[79]	CEI + PCEA (*N* = 29) PIEB + PCEA (*N* = 29)	Nulliparous	Epidural	Epidural test dose of 4 mL 1% lidocaine followed by 10 mL 0.15% ropivacaine	CEI: Continuous infusion of 0.12% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.12% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Epidural test dose of 4 mL 1% lidocaine followed by 10 mL 0.15% ropivacaine	PIEB: Regular boluses of 5 mL 0.12% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.12% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Not specified

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Lin et al., 2016[80]	CEI + PCEA (*N* = 98) PIEB + PCEA (*N* = 99)	Nulliparous	Epidural	Epidural test dose of 4 mL 1% lidocaine followed by 10 mL 0.15% ropivacaine	CEI: Continuous infusion of 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Epidural test dose of 4 mL 1% lidocaine followed by 10 mL 0.15% ropivacaine	PIEB: Regular boluses of 5 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Not specified
Fan et al., 2019[81]	CEI + PCEA (*N* = 1411) PIEB + PCEA (*N* = 1454)	Nulliparous	Epidural	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.125% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ at a rate of 10 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ and lockout interval of 30 min	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.125% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$	PIEB: Regular boluses of 10 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.08% ropivacaine with sufentanil 0.4 $\mu g \cdot mL^{-1}$ and lockout interval of 30 min	Boluses of 5 mL 0.15% ropivacaine
Morau et al., 2019[82]	CEI + PCEA (*N* = 125) PIEB + PCEA (*N* = 124)	Nulliparous	Epidural	Initial bolus of 15 mL 0.1% levobupivacaine with sufentanil 10 μg	CEI: Continuous infusion of 0.1% levobupivacaine with sufentanil 0.36 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 8 mL 0.1% levobupivacaine with sufentanil 0.36 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Initial bolus of 15 mL 0.1% levobupivacaine with sufentanil 10 μg	PIEB: Regular boluses of 8 mL 0.1% levobupivacaine with sufentanil 0.36 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 8 mL 0.1% levobupivacaine with sufentanil 0.36 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5 mL 0.1% levobupivacaine with clonidine 50 μg and sufentanil 0.36 $\mu g \cdot mL^{-1}$
Haidl et al., 2020[22]	CEI + PCEA (*N* = 75) PIEB + PCEA (*N* = 75)	Nulliparous and multiparous	Epidural	Epidural test dose of 5 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ followed by 5 mL of the same solution	CEI: Continuous infusion of 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Epidural test dose of 5 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ followed by 5 mL of the same solution	PIEB: Regular boluses of 5 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and adrenaline 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Discretion of the anesthesiologist

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Ojo et al., 2020[23]	CEI + PCEA (*N* = 59) PIEB + PCEA (*N* = 61)	Nulliparous and multiparous	Epidural	Initial bolus of 20 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 8 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Initial bolus of 20 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	PIEB: Regular boluses of 6 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every 45 min PCEA: Patient-controlled boluses of 8 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5 mL 0.2% ropivacaine and, if required, fentanyl 100 µg
Song et al., 2021[6]	CEI + PCEA (*N* = 78) PIEB + PCEA (*N* = 38)	Nulliparous	Epidural or DPE	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$	CEI: Continuous infusion of 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ at a rate of 8 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Epidural test dose of 3 mL 1.5% lidocaine with adrenaline 5 $\mu g \cdot mL^{-1}$ followed by 10 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$	PIEB: Regular boluses of 8 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with sufentanil 0.3 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Boluses of 5 mL 0.125% ropivacaine
CEI + PCEA vs CI PIEB + PCEA				***CEI + PCEA***		***CI PIEB + PCEA***		
Sia et al., 2007[8]	CEI + PCEA (*N* = 21) CI PIEB + PCEA (*N* = 21)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 2 mL 1.5% lidocaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 2 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min For each potential hourly regular bolus, if no Patient-controlled boluses in previous hour, then bolus of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Boluses of 5 mL 0.2% ropivacaine and, if required, fentanyl 50 µg
Leo et al., 2010[83]	CEI + PCEA (*N* = 31) CI PIEB + PCEA (*N* = 31)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 3 mL 1.5% lidocaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 µg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min For each potential half hourly regular bolus, if no patient-controlled boluses in previous 30 min, then bolus of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$	Boluses of 5 mL 0.2% ropivacaine and, if required, fentanyl 50 µg

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Sia et al., 2013[84]	CEI + PCEA (N = 51) CI PIEB + PCEA (N = 51)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} and lockout interval of 10 min Depending on frequency of patient-controlled boluses, computer-integrated regular boluses of 5 mL 0.1% ropivacaine with fentanyl 2 μg·mL^{-1} at various time intervals	Boluses of 5 mL 0.2% ropivacaine and, if required, fentanyl 50 μg
CEI + PCEA vs CEI + PIEB + PCEA				***CEI + PCEA***		***CEI + PIEB + PCEA***		
Diez-Picazo et al., 2019[85]	CEI + PCEA (N = 53) CEI + PIEB + PCEA (N = 53)	Nulliparous	Epidural	Epidural test dose of 3 mL 0.25% bupivacaine with adrenaline 5 μg·mL^{-1} followed by 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1}	CEI: Continuous infusion of 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PCEA: Patient-controlled boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1} and lockout interval of 20 min	Epidural test dose of 3 mL 0.25% bupivacaine with adrenaline 5 μg·mL^{-1} followed by 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1}	CEI: Continuous infusion of 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PIEB: Regular boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1} every hour PCEA: Patient-controlled boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1} and lockout interval of 20 min	Boluses of 10 mL 0.125% levobupivacaine with fentanyl 1.45 μg·mL^{-1}
Rodriguez-Campoo et al., 2019[86]	CEI + PCEA (N = 95) CEI + PIEB + PCEA (N = 100)	Nulliparous	Epidural	Initial bolus of 10 mL 0.125% levobupivacaine with fentanyl 2 μg·mL^{-1}	CEI: Continuous infusion of 0.0625% levobupivacaine with fentanyl 1 μg·mL^{-1} at a rate of 5 mL·hr^{-1} PCEA: Patient-controlled boluses of 6 mL 0.0625% levobupivacaine with fentanyl 1 μg·mL^{-1} and lockout interval of 20 min	Initial bolus of 10 mL 0.125% levobupivacaine with fentanyl 2 μg·mL^{-1}	CEI: Continuous infusion of 0.0625% levobupivacaine with fentanyl 1 μg·mL^{-1} at a rate of 2 mL·hr^{-1} PIEB: Regular boluses of 7 mL 0.0625% levobupivacaine with fentanyl 1 μg·mL^{-1} every 30 min PCEA: Patient-controlled boluses of 6 mL 0.0625% levobupivacaine with fentanyl 1 μg·mL^{-1} and lockout interval of 20 min	Not specified

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
CEI + PCEA vs remifentanil PCA				***CEI + PCEA***		***Remifentanil PCA***		
Stocki et al., 2014[87]	CEI + PCEA (*N* = 20) Remifentanil PCA (*N* = 19)	Nulliparous and multiparous	Epidural in CEI + PCEA only	Initial bolus of 15 mL 0.1% bupivacaine with fentanyl 50 μg	CEI: Continuous infusion of 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 10 mL 0.1% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	-	Patient-controlled boluses of 20–60 μg and lockout interval of 1–2 min	CEI + PCEA: Boluses of 10 mL 0.1% bupivacaine in first stage of labor or 8 mL 1% lidocaine in second stage of labor
CI CEI + PCEA vs PCEA				***CI CEI + PCEA***		***PCEA***		
Lim et al., 2006[88]	CI CEI + PCEA (*N* = 20) PCEA (*N* = 20)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min Depending on frequency of patient-controlled boluses, computer-integrated continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 0–15 $mL \cdot hr^{-1}$	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 15 min	Boluses of 5 mL 0.2% ropivacaine
CI CEI + PCEA vs CEI + PCEA				***CI CEI + PCEA***		***CEI + PCEA***		
Sng et al., 2009[89]	CI CEI + PCEA (*N* = 30) CEI + PCEA (*N* = 30)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min Depending on frequency of patient-controlled boluses, computer-integrated continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 0–15 $mL \cdot hr^{-1}$	Intrathecal bolus of ropivacaine 2 mg and fentanyl 15 μg Epidural test dose of 3 mL 1.5% lidocaine	CEI: Continuous infusion of 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ at a rate of 5 $mL \cdot hr^{-1}$ PCEA: Patient-controlled boluses of 5 mL 0.1% ropivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 5 mL 0.2% ropivacaine

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
DIEB vs PCEA				***DIEB***		***PCEA***		
Paech et al., 1995[90]	DIEB (N = 85) PCEA (N = 82)	Nulliparous and multiparous	Epidural	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 50 µg followed by 4 mL 0.5% bupivacaine if needed	When required, boluses of 10 mL 0.125% bupivacaine with fentanyl 50 µg	Initial bolus of 10 mL 0.125% bupivacaine with fentanyl 50 µg followed by 4 mL 0.5% bupivacaine if needed	Patient-controlled boluses of 4 mL 0.125% bupivacaine with fentanyl 3 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Boluses of 4 mL 0.5% bupivacaine
Vandermeulen et al., 1995[91]	DIEB (N = 119) PCEA (N = 135)	Nulliparous and multiparous	Epidural	Epidural test dose of 10 mL 0.125% bupivacaine with adrenaline 1.25 $\mu g \cdot mL^{-1}$ and sufentanil 0.75–1 $\mu g \cdot mL^{-1}$	When required, boluses of 10 mL 0.125% bupivacaine with adrenaline 1.25 $\mu g \cdot mL^{-1}$ and sufentanil 0.75–1 $\mu g \cdot mL^{-1}$	Epidural test dose of 10 mL 0.125% bupivacaine with adrenaline 1.25 $\mu g \cdot mL^{-1}$ and sufentanil 0.75–1 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 4 mL 0.125% bupivacaine with adrenaline 1.25 $\mu g \cdot mL^{-1}$ and sufentanil 0.75–1 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Not specified
Nikkola et al., 2006[92]	DIEB (N = 24) PCEA (N = 29)	Nulliparous	Epidural	Initial bolus of 6 mL 0.417% bupivacaine with fentanyl 8.33 $\mu g \cdot mL^{-1}$	When required, boluses of 5–10 mL 0.0625% bupivacaine with fentanyl 7.5 $\mu g \cdot mL^{-1}$	Initial bolus of 6 mL 0.417% bupivacaine with fentanyl 8.33 $\mu g \cdot mL^{-1}$	Patient-controlled boluses of 2 mL 0.0625% bupivacaine with fentanyl 7.5 $\mu g \cdot mL^{-1}$ and lockout interval of 10 min	Not specified
PIEB vs remifentanil PCA				***PIEB***		***Remifentanil PCA***		
Karadjova et al., 2019[93]	PIEB (N = 75) Remifentanil PCA (N = 80)	Nulliparous	Epidural in PIEB only	Epidural test dose of 3 mL 0.25% bupivacaine with fentanyl 50 µg followed by 10 mL 0.1% bupivacaine if needed	Regular boluses of 10 mL 0.0625% bupivacaine with fentanyl 2 $\mu g \cdot mL^{-1}$ every hour	-	Patient-controlled boluses of 0.2–1 $\mu g \cdot kg^{-1}$ and lockout interval of 2 min	PIEB: Boluses of 5 mL 0.1% bupivacaine
PIEB + PCEA vs PCEA				***PIEB + PCEA***		***PCEA***		
Roofthooft et al., 2020[24]	PIEB + PCEA (N = 64) PCEA (N = 61)	Nulliparous	CSE	Intrathecal bolus of ropivacaine 4.8 mg and sufentanil 3 µg	PIEB: Regular boluses of 10 mL 0.12% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ every hour PCEA: Patient-controlled boluses of 5 mL 0.12% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ and lockout interval of 20 min	Intrathecal bolus of ropivacaine 4.8 mg and sufentanil 3 µg	Patient-controlled boluses of 5 mL 0.12% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$ and lockout interval of 12 min	Boluses of 8 mL 0.12% ropivacaine with sufentanil 0.75 $\mu g \cdot mL^{-1}$

Table 1 continued

Reference	Group	Parity	Neuraxial technique	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Method of initiation of neuraxial or systemic analgesia	Technique of maintenance of neuraxial or systemic analgesia	Management of breakthrough pain
Bourges et al, 2021[98]	PIEB + PCEA (N = 155) PCEA (N = 162)	Nulliparous	Epidural	Initial bolus of 3 mL 2% lidocaine followed by 10 mL 0.0625% levobupivacaine with sufentanil 0.5 μg·mL^{-1}	PIEB: Regular boluses of 8 mL 0.0625% levobupivacaine with sufentanil 0.25 μg·mL^{-1} and clonidine 0.375 μg·mL^{-1} every hour PCEA: Patient-controlled boluses of 8 mL 0.0625% levobupivacaine with sufentanil 0.25 μg·mL^{-1} and clonidine 0.375 μg·mL^{-1}and lockout interval of 8 min	Initial bolus of 3 mL 2% lidocaine followed by 10 mL 0.0625% levobupivacaine with sufentanil 0.5 μg·mL^{-1}	Patient-controlled boluses of 8 mL 0.0625% levobupivacaine with sufentanil 0.25 μg·mL^{-1} and clonidine 0.375 μg·mL^{-1}and lockout interval of 8 min	Boluses of 5–10 mL 2% lidocaine or 0.0625% levobupivacaine
PCEA vs fentanyl PCA				***PCEA***		***Fentanyl PCA***		
Halpern et al., 2004[94]	PCEA (N = 124) Fentanyl PCA (N = 118)	Nulliparous	Epidural in PCEA only	Initial bolus of 3–5 mL 0.1% bupivacaine followed by 3–5 mL boluses of the same solution with fentanyl 100 μg if needed	Patient-controlled boluses of 5 mL 0.08% bupivacaine with fentanyl 1.6 μg·mL^{-1} and lockout interval of 10 min	Initial bolus of fentanyl 100 μg followed by boluses of fentanyl 50 μg every 5 min till adequate pain relief	Patient-controlled boluses of 25-50 μg and lockout interval of 10 min	PCEA: Bolus of 5–10 mL 0.125% bupivacaine with fentanyl 50 μg and, if required, 5–10 mL 2% lidocaine
Fentanyl PCA vs remifentanil PCA				***Fentanyl PCA***		***Remifentanil PCA***		
Douma et al., 2010[95]	Fentanyl PCA (N = 54) Remifentanil PCA (N = 52)	Nulliparous and multiparous	-	Initial bolus of 50 μg	Patient-controlled boluses of 20 μg and lockout interval of 5 min	Initial bolus of 40 μg	Patient-controlled boluses of 40 μg and lockout interval of 2 min	Epidural analgesia

CEI = continuous epidural infusion; CI = computer integrated; CSE = combined spinal-epidural; DIEB = demand intermittent epidural bolus; DPE = dural puncture epidural; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PIEB = intermittent epidural bolus

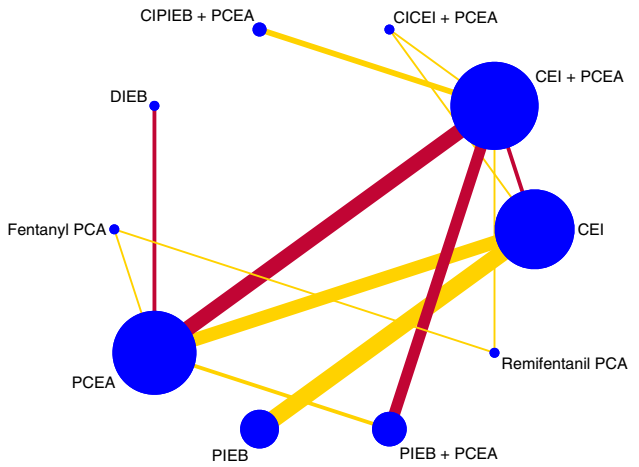

Fig. 3 Network plot of the need for rescue analgesia. Each intervention is depicted by a circle that is proportional in size to the number of patients who were randomized to that intervention. Lines connecting the circles indicate the direct comparisons of interventions, their width proportional to the number of trials evaluating the comparison, and their color representing the average risk of bias. Green, low risk; yellow, some concerns; red, high risk. CEI = continuous epidural infusion; CI = computer integrated; DIEB = demand intermittent epidural bolus; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PIEB = intermittent epidural bolus

Publication bias was not uncovered on evaluation of the comparison-adjusted network plot and with the Egger's test ($P = 0.36$) (Fig. 6). The quality of evidence was graded as low, and the network ranking of interventions was not performed in view of the serious imprecision.

Details of the results of the secondary outcomes are presented in Table 3 (ESM eAppendix 3). Compared with CEI, PIEB decreased the pain score at four hours and the overall duration of labour. Patient-controlled epidural analgesia was inferior to different modes of epidural analgesia with regard to analgesic indices, including PIEB + PCEA for the pain score at two hours, CEI, PIEB, and PIEB + PCEA for the pain score at four hours, and CEI, CEI + PCEA, PIEB, and PIEB + PCEA for the time to rescue analgesia. Further, PCEA lowered the dose of bupivacaine-equivalent local anesthetic per hour relative to CEI and PIEB, and reduced the cumulative dose of bupivacaine-equivalent local anesthetic in labour compared with CEI and CEI + PCEA. The overall duration of labour was lengthened with PCEA relative to PIEB, and the incidence of lower limb motor blockade was lower with PCEA compared with CEI. Patient-controlled epidural analgesia was superior to CEI with respect to the rate of spontaneous vaginal delivery and Cesarean delivery. Relative to CEI + PCEA, PIEB + PCEA reduced pain scores at two hours and four hours, the cumulative dose of bupivacaine-equivalent local anesthetic in labour, and the incidence of lower limb blockade. Computer-integrated CEI + PCEA increased the time to rescue analgesia compared with CEI, CEI + PCEA, CI PIEB + PCEA, PCEA, PIEB and PIEB + PCEA. No differences were present between CI and non CI equivalent modes of equivalent modes of epidural analgesia, other than the increased rate of instrumental delivery with CI CEI + PCEA relative to CEI + PCEA. Fentanyl and/or remifentanil PCA were inferior to various modes of epidural analgesia with respect to pain scores at 30 min, one hour, two hours, and three hours and the overall pain score in labour. Remifentanil PCA decreased the duration of first stage of labour and increased the incidence of oxygen desaturation. Moreover, epidural analgesia was superior to fentanyl and/or remifentanil PCA for the incidence of sedation and nausea and/or vomiting. Compared with fentanyl PCA, remifentanil PCA lowered the pain score at one hour, increased the incidence of pruritus, and reduced the rate of Apgar scores < 7 at one minute.

Discussion

Our systematic review and network meta-analysis demonstrated some differences between modalities for labour analgesia. For the first coprimary outcome, need for rescue analgesia, CEI was inferior to PIEB and PIEB + PCEA was superior to CEI and PCEA but not CEI + PCEA with a low certainty of evidence. The second coprimary outcome, maternal satisfaction, was improved by PIEB + PCEA relative to CEI + PCEA and PCEA alone with a low quality of evidence. Fentanyl PCA increased the requirement for rescue analgesia and decreased maternal satisfaction compared with many methods of delivering epidural solution.

Compared with CEI, PIEB decreased pain scores at four hours, reduced the need for rescue analgesia, and shortened the overall duration of labour, with no other identifiable differences. It is our opinion that the pain score at four hours is an important time point at which the initial method to achieve neuraxial analgesia has faded away and the strategy to maintain sensory blockade is well established. The significance of such time points has been previously recognized by other authors for similar reasons.[101] For a technique of epidural solution delivery to produce optimal analgesia, the fluid must spread well given that the visceral pain in the first stage of labour is mediated by the T10 to L1 spinal segments, and the somatic pain in the second stage of labour is subserved by the S2 to S4 spinal segments.[102] Fluid moves in the epidural space in a nonuniform manner through multiple channels between the dura, fat lobules, nerves, fascia of posterior longitudinal ligament, and the vertebral canal wall.[103] In the case of a

Table 2 Network league table for all interventions in regard to need for rescue analgesia and maternal satisfaction

Need for rescue analgesia

CEI									
1.71 (0.73 to 4.04)	**CEI + PCEA**								
3.41 (0.59 to 19.73)	1.99 (0.34 to 11.76)	**CI CEI + PCEA**							
2.94 (0.66 to 13.01)	1.72 (0.51 to 5.79)	0.86 (0.10 to 7.41)	**CI PIEB + PCEA**						
2.84 (0.44 to 18.37)	1.66 (0.26 to 10.46)	0.83 (0.07 to 10.02)	0.97 (0.11 to 8.78)	**DIEB**					
0.17 (0.03 to 1.15)	**0.10 (0.02 to 0.63)**	**0.05 (0.00 to 0.61)**	**0.06 (0.01 to 0.53)**	**0.06 (0.01 to 0.71)**	**Fentanyl PCA**				
1.21 (0.59 to 2.45)	0.70 (0.37 to 1.34)	0.35 (0.06 to 2.12)	0.41 (0.10 to 1.62)	0.42 (0.08 to 2.39)	**7.01 (1.19 to 41.22)**	**PCEA**			
2.50 (1.31 to 4.77)	1.46 (0.50 to 4.27)	0.73 (0.11 to 4.75)	0.85 (0.17 to 4.30)	0.88 (0.12 to 6.34)	**14.54 (1.96 to 107.57)**	2.07 (0.79 to 5.41)	**PIEB**		
2.97 (1.05 to 8.34)	1.73 (0.85 to 3.52)	0.87 (0.13 to 5.74)	1.01 (0.25 to 4.12)	1.04 (0.15 to 7.11)	**17.26 (2.52 to 118.01)**	**2.46 (1.07 to 5.68)**	1.19 (0.35 to 4.02)	**PIEB + PCEA**	
0.51 (0.05 to 4.99)	0.30 (0.03 to 2.70)	0.15 (0.01 to 2.44)	0.17 (0.01 to 2.15)	0.18 (0.01 to 2.89)	2.96 (0.53 to 16.63)	0.42 (0.05 to 3.77)	0.20 (0.02 to 2.18)	0.17 (0.02 to 1.69)	**Remifentanil PCA**

Maternal satisfaction

CEI									
0.14 (-0.50 to 0.78)	**CEI + PCEA**								
-0.51 (-1.31 to 0.29)	-0.65 (-1.43 to 0.13)	**CI CEI + PCEA**							
-0.63 (-1.68 to 0.43)	-0.76 (-1.60 to 0.08)	-0.11 (-1.26 to 1.03)	**CI PIEB + PCEA**						
-0.32 (-1.06 to 0.42)	-0.46 (-1.26 to 0.35)	0.19 (-0.79 to 1.17)	0.31 (-0.86 to 1.47)	**DIEB**					
0.81 (-0.22 to 1.84)	0.67 (-0.39 to 1.74)	**1.32 (0.11 to 2.54)**	**1.44 (0.08 to 2.79)**	1.13 (-0.04 to 2.31)	**Fentanyl PCA**				
0.14 (-0.42 to 0.70)	0.00 (-0.46 to 0.47)	0.65 (-0.12 to 1.42)	0.76 (-0.19 to 1.72)	0.46 (-0.24 to 1.16)	-0.67 (-1.67 to 0.33)	**PCEA**			
-0.51 (-1.24 to 0.22)	-0.65 (-1.59 to 0.29)	-0.00 (-1.06 to 1.06)	0.11 (-1.14 to 1.37)	-0.19 (-1.21 to 0.83)	**-1.32 (-2.52 to -0.13)**	-0.65 (-1.54 to 0.24)	**PIEB**		
0.34 (-1.17 to 1.84)	0.20 (-1.16 to 1.56)	0.85 (-0.72 to 2.42)	0.96 (-0.64 to 2.56)	0.66 (-0.92 to 2.24)	-0.47 (-2.20 to 1.26)	0.20 (-1.24 to 1.64)	0.85 (-0.80 to 2.50)	**PIEB + DIEB**	
-0.53 (-1.33 to 0.27)	**-0.67 (-1.21 to -0.12)**	-0.02 (-0.94 to 0.91)	0.10 (-0.90 to 1.10)	-0.21 (-1.14 to 0.72)	**-1.34 (-2.50 to -0.18)**	**-0.67 (-1.31 to -0.02)**	-0.02 (-1.07 to 1.03)	-0.87 (-2.33 to 0.60)	**PIEB + PCEA**
-0.19 (-0.81 to 0.44)	-0.32 (-1.10 to 0.45)	0.33 (-0.63 to 1.28)	0.44 (-0.70 to 1.58)	0.13 (-0.78 to 1.05)	**-1.00 (-1.98 to -0.02)**	-0.32 (-1.07 to 0.42)	0.33 (-0.48 to 1.13)	-0.52 (-2.09 to 1.05)	0.34 (-0.57 to 1.26)	**Remifentanil PCA**

Estimates are presented as odds ratios or mean differences with 95% confidence intervals in parentheses. In regard to need for rescue analgesia, odds ratios below 1 favor the column intervention and odds ratios above 1 favor the row intervention. Interventions in bold are significantly different since the 95% confidence interval does not include 1. With respect to maternal satisfaction, mean differences above 0 favor the column intervention and mean differences below 0 favor the row intervention. Interventions in bold are significantly different since the 95% confidence interval does not include 0

CEI = continuous epidural infusion; CI = computer integrated; DIEB = demand intermittent epidural bolus; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PIEB = intermittent epidural bolus

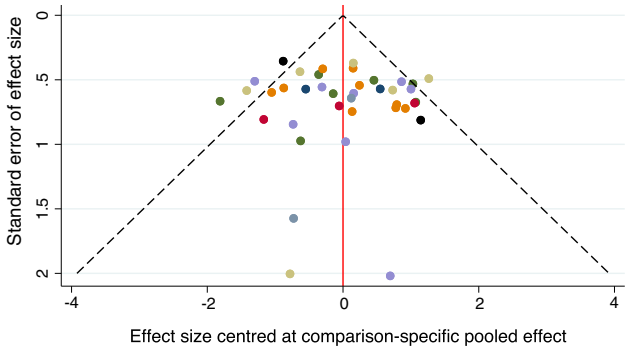

Fig. 4 Comparison-adjusted funnel plot in relation to the network for need for rescue analgesia. Different colors correspond to particular comparisons of interventions. The red line indicates the null hypothesis, which states that the comparison-specific pooled effect estimates do not differ from the respective trial-specific effect sizes

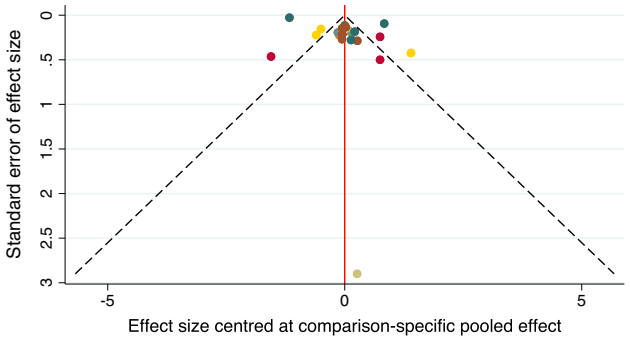

Fig. 6 Comparison-adjusted funnel plot in relation to the network for maternal satisfaction. Different colors correspond to particular comparisons of interventions. The red line indicates the null hypothesis that the comparison-specific pooled effect estimates do not differ from the respective trial-specific effect sizes

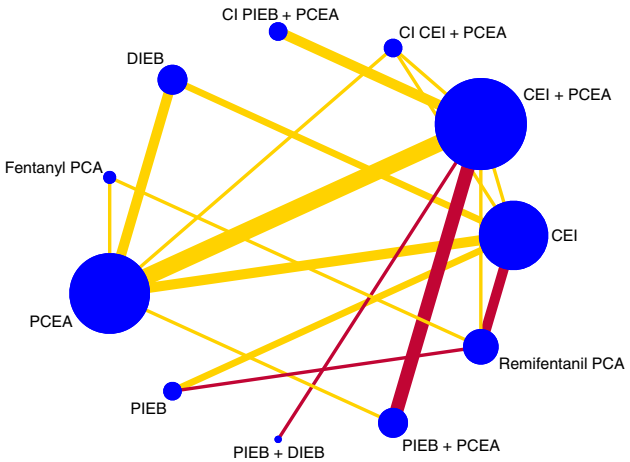

Fig. 5 Network plot with respect to maternal satisfaction. Each intervention is depicted by a circle that is proportional in size to the number of patients who were randomized to that intervention. Connecting lines between the circles indicate the direct comparisons of interventions, their width proportional to the number of trials evaluating the comparison and their color representing the average risk of bias. Green, low risk; yellow, some concerns; red, high risk. CEI = continuous epidural infusion; CI = computer integrated; DIEB = demand intermittent epidural bolus; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PIEB = intermittent epidural bolus

multiorifice epidural catheter, continuous infusion causes flow through only the proximal hole and bolus injection results in flow via the proximal, middle, and distal holes.[104] It is hence likely that the increased efficacy of analgesia with PIEB was due to the increased engagement of channels and the extent and uniformity of spread with bolus rather than continuous infusion administration, as evidenced by previous experimental, animal, and cadaveric models.[103–105] Interestingly, despite the improved analgesia provided by PIEB relative to CEI, it did not increase maternal satisfaction. Maternal satisfaction is complex and not only dependent on pain relief,[106] but also on other factors such as personal expectations, involvement in decision-making, and support from clinical staff.[107,108]

PCEA is an attractive method of delivering epidural solution as it facilitates the autonomy of the parturient to individualize the analgesia as the pattern of labour changes, balancing pain relief with side effects such as motor blockade. Compared with CEI and PIEB, PCEA was inferior for the pain score at four hours and time to rescue analgesia. It did, however, decrease the consumption of local anesthetic, and it is possible that this explains the reduced incidence of lower limb blockade relative to CEI. The motor blockade of the lower limb may correlate with the muscles involved in labour, impairing the capacity and urge to bear down.[101] Compared with CEI, PCEA therefore resulted in an increased and decreased rate of spontaneous vaginal delivery and Cesarean delivery, respectively. In addition to anesthetic practice, variability in institutional and obstetric factors might influence the rate of spontaneous vaginal delivery, instrumental delivery, and Cesarean delivery.[109,110] No differences were revealed between DIEB and PCEA. In view of the significant cost of programmable and sophisticated pumps, DIEB may represent an alternative and appropriate strategy of epidural solution delivery, particularly in developing countries and low resource settings. Considerations relevant to the use of DIEB include the expense and time of clinical staff required for these manual boluses, possibility of infection associated with frequent opening of the closed epidural system,[111] and the potential risk of inadvertent intravenous injection.[112]

Compared with CEI + PCEA, PIEB + PCEA decreased the pain score at two hours and four hours, without lowering the need for rescue analgesia, reduced the consumption of local anesthetic and incidence of lower

Table 3 Conclusion from the results of the analysis and GRADE quality of evidence assessment for the primary and secondary outcomes

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	Conclusions	Quality of evidence	Comments
Parturient							
Pain score at 30 min (0–10)[6,22,24,38,39,43,46,48,51,62,68,72–74,80,90,92,96,99]	19	1,598	8	13	CEI, CEI + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA superior to remifentanil PCA	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Pain score at 1 hr (0–10)[22,24,39,41,43,46–49,51,56,60,62,68,72,74,80,81,90,91,95,96,99]	23	4,893	10	18	CEI superior to DIEB CEI, CEI + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA superior to fentanyl PCA and remifentanil PCA Remifentanil PCA superior to fentanyl PCA	Low quality (⊕⊕)	Downgraded for serious limitations and inconsistency
Pain score at 2 hr (0–10)[6,22,24,38,39,41,43,46–49,51,56,60,62,68,72,74,80,81,90,91,95,96,99]	25	5,013	10	18	PIEB + PCEA superior to CEI, CEI + PCEA, DIEB and PCEA CEI, CEI + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA superior to fentanyl PCA and remifentanil PCA	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Pain score at 3 hr (0–10)[22,24,39,41,43,46,47,51,56,60,62,68,72,74,80,81,90,91,95,96,99]	21	4,700	10	18	CEI, CEI + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA superior to fentanyl PCA and remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score at 4 hr (0–10)[22,24,38,39,41,43,47,51,56,62,72,74,80,81,83,90,91]	17	4,445	10	18	CEI, PIEB and PIEB + PCEA superior to PCEA PIEB superior to CEI, CEI + PCEA and DIEB PIEB + PCEA superior to CEI + PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Overall pain score in labour (0–10)[42,58,61,71,76,92,93]	7	1,901	8	13	CEI and PIEB superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Need for rescue analgesia (%)[6–8,22–24,36–42,47–51,57,58,65,66,68,71–73,76,77,82–84,87,89,91,92,94,95,96,98,97]	40	3,963	13	32	PIEB and PIEB + PCEA superior to CEI PIEB + PCEA superior to PCEA CEI + PCEA, CI CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA, PIEB, and PIEB + PCEA superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

Table 3 continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	Conclusions	Quality of evidence	Comments
Time to rescue analgesia (min)[6,7,38,58,76,83,84]	7	750	7	14	CEI, CEI + PCEA, CI CEI + PCEA, PIEB, and PIEB + PCEA superior to PCEA CI CEI + PCEA superior to CEI, CEI + PCEA, CI PIEB + PCEA, PIEB and PIEB + PCEA	Very low quality (⊕)	Downgraded for serious limitations, imprecision and inconsistency
Dose of bupivacaine-equivalent local anesthetic per h (mg)[6–8,22,23,36,38,43–47,51–54,56,64–71,76,84,85,88–90,98]	32	3,063	13	23	CEI + PCEA, CI CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA and PIEB + PCEA superior to CEI CEI + PCEA superior to CEI + PIEB + PCEA and PIEB CI CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA and PIEB + PCEA superior to CEI + PIEB + PCEA CI PIEB + PCEA, DIEB, PCEA and PIEB + PCEA superior to PIEB DIEB superior to CEI + PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and publication bias
Cumulative dose of bupivacaine-equivalent local anesthetic in labour (mg)[6,24,33,34,37–41,43,45,47,48,50,51,56–58,64,66–69,71–74,76–82,84–86,88,89,91,92,96-98]	44	7,392	13	23	DIEB, PCEA, PIEB and PIEB + PCEA superior to CEI CEI + PCEA superior to CEI + PIEB + PCEA DIEB, PCEA and PIEB + PCEA superior to CEI + PCEA CI CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA, PIEB and PIEB + PCEA superior to CEI + PIEB + PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and publication bias
Duration of first stage of labour (min)[6,37,43,48,54,56,60–64,66,70,73,79–81,83,85,87,92,95]	22	5,449	12	33	Remifentanil PCA superior to CEI, CEI + PCEA, and PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Duration of second stage of labour (min)[6–8,23,33,37,38,42,43,45,48,54,56,57,60–64,66,69,70,73,79–85,87–90,92,94,95,97]	38	7,333	17	38	No differences between interventions	Low quality (⊕⊕)	Downgraded for serious limitations, imprecision and inconsistency
Overall duration of labour (min) [7,8,24,36,38,51,52,58,68,69,71,72,78,84,88,89,98]	17	1,964	12	16	PIEB superior to CEI, CEI + PCEA, CI PIEB + PCEA, DIEB, PCEA, and PIEB + PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

Table 3 continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	Conclusions	Quality of evidence	Comments
Incidence of apnea (%)[63,81,87]	3	3,001	3	3	No differences between interventions	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Incidence of oxygen desaturation (%)[39,62,63,81,87,93,95]	7	3,357	6	9	CEI and PIEB superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Incidence of bradycardia (%)[39,40,50,60,73,81]	6	3,095	5	10	No differences between interventions	Very low quality (⊕)	Downgraded for serious limitations, imprecision and inconsistency
Incidence of sedation (%)[51,55,62,66,74,87,93,94]	8	1,284	9	12	CEI, CEI + PCEA, and PCEA superior to fentanyl PCA CEI, CEI + PCEA and PCEA superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Incidence of nausea and/or vomiting (%)[6–8,22,36,38,39,41,45,48,50,52,54,55,60–63,66–70,73,74,83–85,87–90,92–95,97]	37	4,684	17	38	PCEA superior to fentanyl PCA CEI, CEI + PCEA, and PCEA superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Incidence of pruritus (%)[6–8,22,36,38,39,41,43,45,47,48,50,51,54,55,60–63,65–70,73,74,83–85,87–90,92,93,95,97]	39	4,624	16	39	Fentanyl PCA superior to CEI, CEI + PCEA, CEI + PIEB + PCEA, CI CEI + PCEA, CI PIEB + PCEA, PCEA, PIEB, PIEB + PCEA, and remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations, imprecision and inconsistency
Incidence of shivering (%)[36,38,52,65,69,83–85,88–90]	11	1,130	9	19	No differences between interventions	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Incidence of lower limb motor blockade (%)[6–8,22–24,34–36,40–42,44–52,55,56,65–68,75–77,79,82,85,88,89,94,96–99]	40	4,374	15	40	CEI + PCEA, DIEB, PCEA, and PIEB + PCEA superior to CEI DIEB superior to CEI + PCEA and PIEB PIEB + PCEA superior to CEI + PCEA and PIEB	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

Table 3 continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	Conclusions	Quality of evidence	Comments
Rate of spontaneous vaginal delivery (%)[6–8,22–24,33,36–38,40–48,51–63,65,66,68–77,79,80,82–85,87–92,94,95,96-98]	61	8,263	19	59	CEI + DIEB, DIEB, fentanyl PCA, PCEA, and PIEB + PCEA superior to CEI PIEB + PCEA superior to CEI + PCEA Fentanyl PCA superior to CI CEI + PCEA, PIEB + DIEB and remifentanil PCA DIEB and PIEB + PCEA superior to remifentanil PCA	Low quality (⊕⊕)	Downgraded for serious limitations, imprecision and inconsistency
Rate of instrumental delivery (%)[6–8,22–24,33,36–38,40,41,43–63,65,66,68–70,72–92,94,95,96-98]	64	11,366	19	59	CEI superior to CI CEI + PCEA and PIEB + DIEB CEI + DIEB superior to CEI, CEI + PCEA, CEI + PIEB + PCEA, CI CEI + PCEA and PIEB + DIEB CEI + PCEA superior to CI CEI + PCEA and PIEB + DIEB CI PIEB + PCEA, DIEB, fentanyl PCA, PCEA and PIEB + PCEA superior to CEI + PIEB + PCEA CI PIEB + PCEA, DIEB, fentanyl PCA, PCEA, PIEB, PIEB + PCEA and remifentanil PCA superior to CI CEI + PCEA CI PIEB + PCEA, DIEB, fentanyl PCA, PCEA, PIEB, PIEB + PCEA and remifentanil superior to PIEB + DIEB DIEB superior to CEI and CEI + PCEA Fentanyl PCA superior to CEI and CEI + PCEA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of Cesarean delivery (%)[6–8,22–24,33,34,36–38,40–63,65,66,68,69,71–73,75–77,79,80,83–85,87–91,93–95,96-98]	61	8,294	20	58	CEI + PCEA, PCEA, PIEB + DIEB and PIEB + PCEA superior to CEI CEI + PCEA and PIEB + PCEA superior to remifentanil PCA	Very low quality (⊕)	Downgraded for serious limitations, imprecision and inconsistency

Table 3 continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	Conclusions	Quality of evidence	Comments
Satisfaction (0–10)[6–8,24,36,38,51,52,57,60,62,63,66,69,72,73,75,76,81–84,87–89,92–95]	29	5,779	18	37	PIEB + PCEA superior to CEI + PCEA and PCEA CI CEI + PCEA, CI PIEB + PCEA, PIEB, PIEB + PCEA and remifentanil PCA superior to fentanyl PCA	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Fetal and neonatal							
Rate of bradycardia (%)[6,36,38,43,63,69,83,84,88,89,94]	11	1,170	9	27	No differences between interventions	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Umbilical pH[24,47,49,52,54,60–63,67,68,70,74,85,87,93–95]	18	2,622	12	24	No differences between interventions	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Rate of Apgar score < 7 at 1 min (%)[24,34,43–45,47,52–54,56,60,61,65–68,73,74,78,81,90,91,94]	23	6,126	9	12	CEI, PCEA, and remifentanil PCA superior to fentanyl PCA	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Rate of Apgar score < 7 at 5 min (%)[7,8,24,34,36,38,40,43–45,47,52–54,56,60,61,63,64,66,74,78,81,90,91,94]	26	6,292	13	32	No differences between interventions	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

CEI = continuous epidural infusion; CI = computer integrated; DIEB = demand intermittent epidural bolus; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; PIEB = intermittent epidural bolus

limb motor blockade, and increased maternal satisfaction. This superiority of PIEB + PCEA may reflect the synergistic effect of these two methods of bolus administration in improving the extent and uniformity of spread. The decreased motor blockade of the lower limb translated into the increased rate of spontaneous vaginal delivery with PIEB + PCEA. Relative to CEI + PCEA, the use of CI CEI + PCEA resulted in a greater time to rescue analgesia, probably by increasing the rate of infusion of CEI with the frequency of PCEA boluses, and a higher rate of instrumental delivery, but no differences were shown between CI PIEB + PCEA and PIEB + PCEA.

Fentanyl and remifentanil PCA were inferior to all methods of delivering epidural solution in relation to the pain scores at 30 min and at one hour, two hours, and three hours, with a difference of as much as almost six on a pain scale out of ten. If it were possible to match the peak effect of remifentanil to the uterine contractions, then remifentanil may in theory be more effective for labour analgesia, although this is difficult in clinical practice as its effect-site concentration is highest at one to two minutes, while the uterine contraction might only last 60–80 sec.[113] Compared with strategies of delivering epidural solution, the use of fentanyl and remifentanil PCA increased the pain scores as labour progressed, possibly indicative of more severe mechanisms of pain in later labour or of opioid-induced hyperalgesia. Remifentanil PCA was, however, superior to fentanyl PCA with respect to the pain score at one hour. Relative to various methods of delivering epidural solution, fentanyl and remifentanil PCA were associated with increased sedation and nausea and vomiting, fentanyl PCA decreased pruritus, and remifentanil PCA increased the incidence of oxygen desaturation. Remifentanil PCA was not found to increase the risk of apnea, but none of the included trials were powered for adverse events. Such undesirable occurrences were uncommon and lack of evidence of harm is not the same as evidence of absence of harm. The potential of remifentanil to result in apnea, bradycardia, and respiratory and cardiac arrest has been underlined in numerous case reports and surveys.[114–118] In terms of neonatal outcomes, fentanyl PCA when compared with PCEA and remifentanil PCA increased the rate of Apgar scores < 7 at one minute, but it is important to note that this does not correlate with individual infant outcomes.[119] Overall, despite its limitations relative to strategies of delivering epidural solution, remifentanil PCA was found to be superior to fentanyl PCA for analgesic indices. We opine that it should be considered in circumstances where neuraxial techniques are contraindicated, and only when safety can be maintained, in other words with one-on-one midwifery care, availability of supplemental oxygen, and the use of monitors for oxygenation and ventilation.

Our network meta-analysis is not comparable with other systematic reviews that pooled disparate interventions such as CEI, CEI + PCEA, and CI CEI + PCEA and PIEB, PIEB + PCEA, and CI PIEB + PCEA.[13–16] Compared with a meta-analysis which evaluated CEI to PCEA,[11] our findings are similar, although these results revealed differences in the mode of delivery between these two methods of delivering epidural solution. The findings for CEI + PCEA *vs* PIEB + PCEA from this meta-analysis are comparable to those from a previous one,[18] but we did not uncover any difference in the rate of instrumental delivery. Unlike the systematic reviews that examined epidural analgesia relative to remifentanil PCA,[19–21] the magnitude of the difference in the pain score at two hours was greater in this meta-analysis and the incidence of nausea and/or vomiting was higher with remifentanil. Moreover, we were able to add to the current evidence with the findings related to the pain score at three hours and the incidence of sedation. It is likely that some of the differences in the results were a reflection of the increased number of randomized controlled trials included in our systematic review, and the use of network meta-analysis to substitute or supplement direct comparisons with indirect ones.

Several limitations limit the findings of this systematic review. First, in our definition of PIEB, we did not distinguish between manual and automated programmed administration. It is possible that the automated delivery of scheduled epidural solution may be superior to manual administration or vice versa. Second, concerns were present with regard to the presence of bias in all trials and were particularly associated with the randomization process, deviations from intended interventions, and the selection of the reported result. Third, specific subgroups in the obstetric population, such as those with preeclampsia, were excluded and the results should not thus be generalized to their management in labour. Fourth, heterogeneity was present in the method of initiation of neuraxial or systemic analgesia and the nature, concentration, and dose of local anesthetic and opioid. Fifth, the initial strategy to achieve rather than maintain neuraxial analgesia was likely to influence the pain score at 30 min. Sixth, standardization was not present in the definition of outcomes such as motor blockade. Last, concerns related to imprecision for many outcomes precluded the ranking of studied interventions.

In conclusion, the results from this systematic review and network meta-analysis indicate that PIEB improves analgesic efficacy compared with CEI, and that PCEA decreases local anesthetic consumption at the expense of inferior analgesia relative to CEI and PIEB. Compared with CEI, PCEA reduces the incidence of lower limb motor blockade, increasing and decreasing the rate of spontaneous vaginal delivery and Cesarean delivery,

respectively. No differences were found between PCEA and DIEB. Of significance, PIEB + PCEA has emerged as superior to CEI + PCEA with regard to the analgesic indices, consumption of local anesthetic, incidence of lower limb motor blockade, rate of spontaneous vaginal delivery, and the maternal satisfaction. Computer-integrated CEI + PCEA increases the time to rescue analgesia compared with CEI + PCEA while the results show no differences between CI PIEB + PCEA and PIEB + PCEA. Fentanyl and remifentanil PCA do not provide the same level of analgesia as all methods of delivering epidural solution, and analgesic ineffectiveness is increased with time spent in labour. They predispose to a higher incidence of side effects such as nausea and/or vomiting and sedation and, despite the results show remifentanil to be superior to fentanyl PCA for analgesia at an early time point, the former increases the incidence of oxygen desaturation relative to other strategies of delivering epidural solution. Overall, we interpret the findings of our systematic review as suggesting PIEB + PCEA to be the optimal delivery mode, although the potential differing importance of the various maternal, fetal, and neonatal outcomes in determining which is optimal has not, to our knowledge, been elucidated yet. In view of the extensive range of modalities for labour analgesia, further high-quality and large randomized controlled trials are required.

Author contributions *Simon Wydall* was involved in the design of the meta-analysis, screening of results, data extraction, and the drafting of the manuscript. *Danaja Zolger* was involved in the data extraction and the quality of evidence assessment. *Adetokunbo Owolabi* was involved in the risk of bias assessment and the drafting of the manuscript. *Bernadette Nzekwu* was involved in the data extraction. *Desire Onwochei* was involved in the design of the meta-analysis, search strategy, risk of bias assessment, and the revision of the manuscript. *Neel Desai* was involved in the design of the meta-analysis, search strategy, screening of results, data extraction, quality of evidence assessment, statistical analysis, and the drafting and revision of the manuscript.

Acknowledgements The authors would like to thank Dr Ryan Howle, consultant anesthetist at Coombe Women and Infants University Hospital, for reading the manuscript and providing constructive comments.

Disclosures None declared.

Funding statement This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Editorial responsibility This submission was handled by Dr. Ronald B. George, Associate Editor, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*.

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