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REPORTS OF ORIGINAL INVESTIGATIONS

The effects of epidural/spinal opioids in labour analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials

Effets des opioïdes en péridurale/rachi pour l'analgésie du travail sur les aboutissements des nouveau-nés: une méta-analyse des études randomisées et contrôlées

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Abstract

Purpose *Epidural/spinal opioids are increasingly used to relieve parturients' pain in labour. Some studies indicate that opioids can induce side effects in neonates, such as respiratory depression and neurobehavioural changes. This meta-analysis aimed to clarify the effects of opioids in labour analgesia on neonates.*

Source *PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE™ were searched for relevant randomized controlled trials (RCTs). The neonatal data of Apgar scores, Neurological and Adaptive Capacity Scores (NACS), and umbilical cord pH values were extracted. Statistical analyses were carried out using Review Manager 5.2 and Stata® 10.*

Principal findings *Twenty-one trials with 2,859 participants were included in our meta-analysis. No difference in the incidence of Apgar scores < 7 was shown between the opioid and control groups at one minute (risk difference [RD] 0.0%, 95% confidence interval [CI]: −3.0 to 2.0, $P = 0.78$; $I^2 = 0\%$, 95% CI: 0 to 50) and at five minutes (RD −1.0%, 95% CI: −2.0 to 1.0, $P = 0.31$; $I^2 = 0\%$, 95% CI: 0 to 50). No significant differences were found in the NACS at two hours (mean difference [MD] −0.35, 95% CI: −1.70 to 1.01, $P = 0.62$; $I^2 = 0\%$, 95% CI: 0 to 79) and at 24 hr (MD −0.45, 95% CI: −1.36 to 0.46, $P = 0.33$; $I^2 = 3\%$, 95% CI: 0 to 26). Also, no significant differences were found in umbilical cord artery pH (MD −0.02, 95% CI: −0.06 to 0.03,*

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P = 0.48; I^2 = 80%, 95% CI: 46 to 92) and vein pH (MD −0.03, 95% CI: −0.07 to 0.00, P = 0.08; I^2 = 77%, 95% CI: 36 to 91). No significant publication bias was found.

Conclusion *The common doses of fentanyl and sufentanil used with an epidural/spinal technique in labour analgesia are safe for neonates up to 24 hr after delivery. In future studies, more attention should be paid to the long-term side effects in neonates.*

Résumé

Objectif *Les opioïdes administrés par péridurale/rachi sont de plus en plus souvent utilisés pour soulager la douleur du travail chez les parturientes. Quelques études indiquent que les opioïdes peuvent induire des effets indésirables chez les nouveau-nés, tels qu'une dépression respiratoire et des changements neurocomportementaux. Cette méta-analyse visait à clarifier les effets des opioïdes administrés pour l'analgésie du travail sur les nouveau-nés.*

Source *Les essais cliniques randomisés pertinents ont été recherchés dans les bases de données Cochrane Central Register of Controlled Trials (CENTRAL) et EMBASE™. Les données néonatales des scores d'Apgar, les scores NACS (Neurological and Adaptive Capacity Scores) et les valeurs du pH du cordon ombilical en ont été extraits. Les analyses statistiques ont été réalisées à l'aide de Review Manager v.5.2 et de Stata® 10.*

Constatations principales *Vingt et une études regroupant 2 859 participantes ont été incluses dans notre méta-analyse. Aucune différence dans l'incidence des scores d'Apgar < 7 n'a été montrée entre le groupe opioïdes et le groupe contrôle à une minute (différence de risque [DR] 0,0 %, intervalle de confiance [IC] à 95 %: −3,0 à 2,0, P = 0,78; I^2 = 0 %, IC à 95 %: 0 à 50) et à cinq minutes (DR −1,0 %, IC à 95 %: −2,0 à 1,0, P = 0,31; I^2 = 0 %, IC à 95 %: 0 à 50). Il n'y a pas eu de différence significative pour le NACS à 2 heures (différence moyenne [DM] −0,35, IC à 95 %: −1,70 à 1,01, P = 0,62; I^2 = 0 %, IC à 95 %: 0 à 79) et à 24 h (DM −0,45, IC à 95 %: −1,36 à 0,46, P = 0,33; I^2 = 3 %, IC à 95 %: 0 à 26). De même, aucune différence significative n'a été trouvée pour le pH artériel du cordon ombilical (DM −0,02, IC à 95 %: −0,06 à 0,03, P = 0,48; I^2 = 80 %, IC à 95 %: 46 à 92) et pour le pH veineux (DM −0,03, IC à 95 %: −0,07 à 0,00, P = 0,08; I^2 = 77 %, IC à 95 %: 36 à 91). Aucun biais significatif de publication n'a été identifié.*

Conclusion *Les doses habituelles de fentalyl et sufentanil utilisées dans les techniques péridurales/rachi pour l'analgésie du travail sont sécuritaires pour les nouveau-nés jusqu'à 24 heures après l'accouchement. Davantage d'intérêt devra être porté aux effets secondaires à long terme chez les nouveau-nés au cours des futures études.*

Labour pain has been considered to be one of the most unbearable pain experiences,[1] and many women sustain long-term emotional and psychological effects following childbirth.[2] A number of medical procedures have been introduced for pain relief, such as epidural/spinal analgesia, pudendal nerve block, and paracervical blockade. Epidural/spinal analgesia, including epidural analgesia (EA), combined spinal/epidural analgesia, and spinal analgesia are considered to be the most effective procedures.[3] With epidural/spinal labour analgesia, local anesthetics (e.g., bupivacaine and ropivacaine) are most commonly used. In addition, the opioids (e.g., meperidine, fentanyl, sufentanil, and remifentanil) are also added to improve the quality of analgesia because of their earlier onset and superior pain relief.[4] Nevertheless, the use of opioids for labour analgesia is currently controversial because of the potentially negative effects on neonates.

It is known that opioids can pass easily through the placenta and induce opioids-related effects on newborns. Respiratory depression is probably the most serious side effect induced by opioids. This manifests by minute volume reduction,[5] a decrease in oxygen saturation,[6] and respiratory acidosis.[7] In addition, alterations in neonatal neurobehaviour[8] and decreases in the variability of the fetal heart rate[9] induced by opioids are also harmful. Among these opioids, meperidine is reported to be the most widely used for labour analgesia[10] despite evidence that indicates its limited efficacy and degree of side effects.[11] Fentanyl and sufentanil are synthetic opioids which appear to be significantly safer and have less negative impact on neonates.[12-14] Nevertheless, some studies[15-17] suggest that these synthetic opioids are far from ideal.[18-20] Nakamura *et al.*[15] reported that the use of sufentanil in labour analgesia caused increased pruritus and poor outcomes in newborns when compared with those of the controls. Tian *et al.*[13] reported that intrathecal sufentanil is safe for both mothers and newborns; however, sometimes it can induce a rise in maternal temperature during labour.

Neonatal outcome is one of the most important concerns relating to labour analgesia. The routine methods to assess the impact of labour analgesia on neonates include a lower Apgar score,[13,15,21,22] a lower umbilical artery (UA) or vein (UV) pH value,[16,17,23] and a lower Neurological and Adaptive Capacity Score (NACS).[24,25] The NACS is a systemic assessment of neonates[26] that evaluates five general aspects: adaptive capacity, passive tone, active

tone, primary reflexes, and general neurologic status. Systematic reviews have been conducted in an attempt to pool all the data to facilitate analysis of different methods and different anesthetic drugs on the degree of patient satisfaction and the efficacy of labour analgesia.[4,27,28] A meta-analysis was conducted to assess the effect of non-axial administration of fentanyl on neonatal outcome;[29] however, a quantitative analysis was not conducted, and an evaluation of intrathecal fentanyl was not included.

The objective of this meta-analysis was to include randomized controlled trials (RCTs) addressing epidural/spinal opioids for labour analgesia in order to evaluate their effect on neonatal outcomes. The primary outcome measures were Apgar scores, NACS, and UA/UV pH values. We also attempted to examine patient satisfaction and side effects.

Methods

Search strategy

We searched PubMed (1966 to Oct 2013), EMBASE™ (1966 to Oct 2013), and the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2013) without language restriction for trials assessing the effects of labour analgesia with opioids on neonatal outcome. The latest search was explicitly updated to Oct 20, 2013. The search strategies included combinations of the following text words: ('analgesia' OR 'anesthesia') AND ('obstetrical' OR 'pregnancy' OR 'labor') AND ('neonate' OR 'neonatus' OR 'newborn' OR 'infant') AND ('epidural' OR 'combined spinal epidural' OR 'spinal' OR 'intrathecal') AND ('opioids' OR 'fentanyl' OR 'sufentanil' OR 'remifentanil' OR 'morphine' OR 'alfentanil'). The reference lists of the reviews, original reports, case reports, letters to the editor, conference abstracts (Index to Scientific & Technical Proceedings database, 2002 to Oct 2013), and meta-analyses involving the effects of labour analgesia with opioids on the outcomes of neonates were also scanned to avoid missing trials not yet included in the databases.

Study selection

The selection criteria for this meta-analysis were as follows: 1) study design: RCT; 2) participants: healthy women in labour (nulliparous and parous) under epidural/spinal analgesia; 3) interventions: epidural/spinal opioids combined with local anesthetic compared with only local anesthetic administration; 4) outcome variables - at least one of the following was reported: Apgar scores, NACS, UA/UV pH values. Studies were excluded where two arms of the comparison both used opioids in the labour analgesia procedure. Two reviewers (W.K., C.L.) independently evaluated the eligibility of all trials which trended for inclusion in this meta-analysis. Any nonconformity was checked by another author (S.L.Q.).

Data extraction

Two researchers (W.K., C.L.) independently extracted data from the included trials using a predesigned table. Data extraction included publication years, authors of each study, number and age of the participants, technique and drugs of the labour analgesia, visual analogue pain scale (VAPS) of the parturients, and outcomes of the neonates. Graphic digitizing software (Engauge Digitizer version 3.0, http://digitizer.sourceforge.net/) was used to extract data shown in the figures. Any nonconformity was resolved by discussion among all authors.

Qualitative assessment

The quality of all the included studies was appraised using the guidelines recommended by the Cochrane Collaboration.[30] The risk of bias was evaluated in six categories: randomization and sequence generation, blinding method, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Every category was assessed according to three rulings: low risk, unclear risk, and high risk. Each of the included trials was assigned a classification of quality on the basis of the *Cochrane Handbook* (Table 8.7.a). The items of randomization and sequence generation, blinding method, and allocation concealment were considered as key domains and the evaluation was as follows: low risk of bias (low risk of bias for all key domains); unclear risk of bias (unclear risk of bias for one or more key domains); and high risk of bias (high risk of bias for one or more key domains). Two authors (W.K., C.L.) independently evaluated the quality of the trials. Any disagreement about the appraisal was resolved by discussion among all authors.

Statistical analysis

The primary outcome measures were Apgar scores, NACS, and UA/UV pH values. Secondary outcomes included VAPS score after labour analgesia and side effects of parturients (motor block, vomiting, pruritus, nausea, sedation, and hypotension). All outcomes were included in the meta-analysis to assess the safety of opioids on neonates and parturients in labour analgesia.

For dichotomous outcomes, we calculated risk differences (RD) and corresponding 95% confidence

intervals (CIs) for each trial separately and then pooled the estimates with a fixed-effect model using the Mantel-Haenszel method. We chose a fixed-effect model as it provides a less biased estimate when an outcome is rare, even under conditions of heterogeneity.[31,32] For continuous outcomes, we calculated mean differences (MD) and corresponding 95% CIs for each trial separately and then pooled the estimates using a random effects model. We chose a random effects model to account for the clinical and methodological heterogeneity between studies. If the measurement scale was not consistent across studies, we used standardized mean differences (SMD). The mean and standard deviation were calculated when continuous outcomes were summarized as interquartile range, median, and range (Appendix). Statistical heterogeneity was quantified using the I^2 statistic. All reported P values are two-sided. Review Manager 5.2 (Cochrane Collaboration, Oxford, UK) and Stata® 10.0 (Stata Corp, College Station, TX, USA) were used to perform the statistical analysis.

Sensitivity analysis and publication bias

A sensitivity analysis was performed to assess whether inclusion of the high-risk studies could significantly bias the result. The subgroups were conducted according to high and not high risk of bias (including low and unclear risk of bias). To visually assess the potential for publication bias, we constructed a funnel plot for the outcome of Apgar scores at one minute, which involved most of the included trials.

Results

Study selection

The search of PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) initially yielded 552 trials. The search strategy was presented in a flow diagram (Fig. 1). Initially, 371 trials were discarded because they were not RCTs or they were duplicates of other studies. After reviewing the abstracts of the remaining 181 trials, 146 were excluded because the trials were either not relevant to our study or both groups used opioids. After reviewing the full texts for a detailed evaluation,14 of the remaining 35 trials were excluded as no endpoint of interest was reported, and in three of these trials, the full text was not found: one in German,[33] one in Spanish,[34] and one in French.[35] Finally, 21 trials[13,15-17,21-23,36-49] that met the criteria were included in the meta-analysis. No additional studies, unpublished relevant trials, or abstracts of meetings were obtained.

Study characteristics

The characteristics of these included trials are shown in Table 1. The 21 RCTs comprised 2,859 participants, 1,443 with opioids added to labour analgesia and 1,416 with only local anesthetic. All participants were healthy with American Society of Anesthesiologists physical status I or II and without a history of drug abuse, opioid use, opioid allergy, or other complications. The labour analgesia was usually begun during active first-stage labour. The control group received only a local anesthetic such as bupivacaine, ropivacaine, or lidocaine, and the opioid group received a combination of local anesthesia and opioids. Eight trials reported the total opioid dose.[16,17,22,23,40,42-44] Among these, the fentanyl dose was 100-500 μg for EA and up to 1,500 μg for patient-controlled intravenous analgesia; meanwhile, the sufentanil dose for EA was 7.5-30 μg.

Synthesis of results

Apgar scores at one minute

Eighteen trials[1,13,15-17,23-46] compared the incidence of Apgar scores < 7 at one minute after delivery; these trials comprised 1,290 women in the opioid group and 1,300 women in the control group (Fig. 2). There was no significant difference between the opioid and control groups (RD 0.0%, 95% CI: −3.0 to 2.0, $P = 0.78$), which suggested that the use of opioids for labour analgesia did not influence the neonatal outcome of Apgar scores at one minute. With the subgroup analysis, no significant difference was found between the not high (the low and unclear) and high risk of bias groups ($P = 0.80$). No significant heterogeneity was found in these trials ($I^2 = 0\%$, 95% CI: 0 to 50).

Apgar scores at five minutes

The 18 trials comprised 1,290 women in the opioid group and 1,300 women in the control group.[21-23,36-46] These trials compared the incidence of Apgar scores < 7 at five minutes (Fig. 3). No significant difference was found between the two groups (RD −1.0%, 95% CI: −2.0 to 1.0, $P = 0.31$), which indicated that opioids did not have a significant effect on the neonates. No differences were detected between the subgroups ($P = 0.95$). No significant heterogeneity was found among these trials ($I^2 = 0\%$, 95% CI: 0 to 50).

Neurological and Adaptive Capacity Scores at two hours

Five trials[15-17,23,40] comprising 141women in the opioid group and 135 women in the control group compared NACS at two hours (Fig. 4). These studies found that the

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Study	Comparison	*n*	Mean Age (yr)	Birth Weight (g)*	Anesth Method	Labour Analgesia Procedure	Dose of Opioids*	VAPS*	Block Level	Risk of bias						Rank
										R	B	A	C	F	O	
Tian *et al.*2013[13]	S	37	28.5	NA	SA	Sufentanil 6 μg in 1.5 mL; then 2 mL·hr^{-1} (2 μg·mL^{-1}) with a 15 min lockout interval of 1 mL bolus.	NA	(0-100) 15 (13)	T10	L	U	U	L	L	U	U
	C	38	28.2	NA	no	Non-pharmacological method.		86 (11)	T10							
Nakamura *et al.*2009[15]	S	20	21.4	3,130 (254)	CSEA	0.5% bupivacaine 0.5 mL + sufentanil 5 μg intrathecally; if needed, a bolus of 0.125% ropivacaine 6 mL epidurally.	NA	(0-10) 1.25 (1.25)	NA	L	L	H	H	L	U	H
	C	20	19.9	3,341 (530)	EA	0.125% ropivacaine 15 mL epidurally; if needed, a bolus of 0.125% ropivacaine 6 mL epidurally.		2.25 (2.25)	NA							
Marcos *et al.*2008[47]	F	32	31	NA	EA	25 μg fentanyl, followed by infusion of 0.2% ropivacaine 7 mL·hr^{-1}	NA	no difference	T10	U	H	U	H	L	U	H
	C	32	29.9	NA	EA	0.25% bupivacaine 1 mL, followed by infusion of 0.2 % ropivacaine 7 mL·hr^{-1}			T10							
Salim *et al.*2005[21]	F	63	25.7	3,147 (314)	EA	A basal continuous infusion of 0.125% bupivacaine + 2 μg·mL^{-1} fentanyl at a rate of 8 mL·hr^{-1}; with a 20 min lockout interval of 3 mL bolus.	NA	no difference	NA	L	U	U	L	L	U	U
	C	64	25.6	3,255 (467)	EA	Intermittent bolus infusions of 10 mL of 0.25% bupivacaine on demand with minimal intervals of 60 min.			NA							
Beilin *et al.*2005[22]	F	59	36	NA	EA	Initiated with 0.25% bupivacaine 10 mL, maintained with 0.0625% bupivacaine + 2 μg·mL^{-1} fentanyl at a rate of 10 mL·hr^{-1}.	70 μg (20-350)	NA	NA	L	L	L	H	L	L	L
	C	60	35	NA	EA	0.25% bupivacaine 10 mL, maintained with 0.125% bupivacaine at a rate of 10 mL·hr^{-1}.		NA	NA							
Pace *et al.*2004[36]	F	55	28	NA	SA	2.5 mg bupivacaine + 25 μg fentanyl + 1 mL 10% glucose intrathecally.	NA	(0-4) 0.15 (0.36)	NA	U	L	H	L	L	U	H
	C	56	30	NA	pudendal block	2% mepivacaine 7 mL in each side of pudendal nerve block.		2.21 (0.95)	NA							

Table 1 continued

Study	Comparison	*n*	Mean Age (yr)	Birth Weight (g)*	Anesth Method	Labour Analgesia Procedure	Dose of Opioids*	VAPS*	Block Level	Risk of bias						Rank
										R	B	A	C	F	O	
Lee *et al.*2002[37]	F	20	27	3,210 (440)	EA	0.1% ropivacaine + 2 μg·mL^{-1} fentanyl 10 mL·hr^{-1}; 5-10 mL·hr^{-1} 0.2% ropivacaine with at least a 20 min interval.	NA	(0-100) 23.2 (14.8)	T6	L	L	L	H	L	L	L
	C	19	27	3,320 (540)	EA	0.1% ropivacaine 10 mL·hr^{-1}; 5-10 mL·hr^{-1} 0.2% ropivacaine with at least a 20 min interval.		25.6 (15)	T6							
Ruban *et al.*2000[38]	F	15	29.2	3,249 (321)	EA	0.2% ropivacaine 10 mL; 0.125% ropivacaine + 2 μg·mL^{-1} fentanyl 5 mL on demand, with a lockout interval of 10 min.	NA	(0-100) 13.9 (5.5)	T8	U	U	H	L	L	L	H
	C	17	29.5	3,276 (305)	EA	0.2% ropivacaine 10 mL; 0.125% ropivacaine 5 mL on demand, with a lockout interval of 10 min.		15.3 (6.2)	T7							
Nikkola *et al.*2000[23]	F	5	20-36	3,890 (364)	PCIA	50 μg fentanyl every five minutes until pain was relieved or side effects appeared, then a bolus of 50 μg fentanyl with a lockout of five minutes.	610 μg (150-1,500)	NA	NA	U	L	H	U	L	L	H
	C	7	20-36	3,834 (397)	paracervical blockade	10 mL of 0.25% bupivacaine injected into four locations at cervix.		NA	NA							
Porter *et al.*1998[17]	F	68	27.9	3,500 (500)	EA	0.25% bupivacaine 8-10 mL; 0.0625% bupivacaine with 2.5 μg·mL^{-1} fentanyl to maintain a sensory level at T8-T10.	183 (75) μg	NA	T8-10	L	L	L	H	L	U	L
	C	70	28.5	3,400 (500)	EA	0.25% bupivacaine 8-10 mL; 0.125% bupivacaine to maintain a sensory level at T8-T10.		NA	T8-10							
Claes *et al.*1998[40]	S	25	29.5	3,409 (422)	EA	0.125% bupivacaine 10 mL + 12.5 μg epinephrine + 7.5 μg sufentanil.	7.5?	(0-100) 0.5 (0.2)	T10	U	L	U	H	U	U	U
	C	25	27	3,200 (400)	EA	0.125% bupivacaine 10 mL + 12.5 μg epinephrine.		2.7 (0.8)	T10							
Olofsson *et al.* 1998[39]	S	422	30	3,566	EA	Bupivacaine 1.25 mg·mL^{-1} 6 mL + sufentanil 5 pg·mL^{-1} 2 mL = 8 mL; boluses were given as bupivacaine 1.25 mg·mL^{-1} 6 mL and every second time with 10 pg·mL^{-1} sufentanil.	NA	NA	NA	L	H	L	H	L	L	H
	C	435	29	3,517	EA	Bupivacaine 2.5 mg·mL^{-1} + adrenaline 5 pg·mL^{-1} = 6 mL; boluses were given as bupivacaine 2.5 mg·mL^{-1} and adrenaline 5 pg·mL^{-1} = 6 mL.		NA	NA							

Table 1 continued

Study	Comparison	*n*	Mean Age (yr)	Birth Weight (g)*	Anesth Method	Labour Analgesia Procedure	Dose of Opioids*	VAPS*	Block Level	Risk of bias						Rank
										R	B	A	C	F	O	
Loftus *et al.*1995[16]	F	14	29	3,461 (197)	EA	Bolus of 0.125% bupivacaine + 75 μg fentanyl 12 mL followed by 0.125% bupivacaine + fentanyl 1.5 $\mu g \cdot mL^{-1}$ 10 $mL \cdot hr^{-1}$.	136.6 (13.1)μg	(0-100) 15.3 (6.1)	T8	L	L	L	H	U	L	L
	C	13	27	3,689 (148)	EA	Bolus of 0.25% bupivacaine 12 mL followed by 0.125% bupivacaine 10 $mL \cdot hr^{-1}$.		15.4 (5.8)	T8							
	S	9	28	3,569 (159)	EA	Bolus of 0.125% bupivacaine + 15 μg sufentanil 12 mL followed by 0.125% bupivacaine with sufentanil 0.25 $\mu g \cdot mL^{-1}$ 10 $mL \cdot hr^{-1}$.	23.8 (1.8) μg	3.1 (2.1)	T8							
	C	13	27	3,689 (148)	EA	Bolus of 0.25% bupivacaine 12 mL followed by 0.125% bupivacaine 10 $mL \cdot hr^{-1}$.		15.4 (5.8)	T8							
Steinberg *et al.*1992[41]	S	19	24.7	3,433 (536)	EA	1.5 $\mu g \cdot mL^{-1}$ sufentanil in 0.125% bupivacaine 10 mL.	NA	(0-100) 10.6 (4.2)	NA	U	U	U	H	U	L	U
	C	24	26	3,524 (495)	EA	0.25% bupivacaine 10 mL.		36.1 (10.2)	NA							
Vertommen *et al.*1991[42]	S	348	29	3,400 (300)	EA	0.125% bupivacaine 10 mL + 12.5 μg epinephrine + 10 μg sufentanil.	30 μg	1.1% dissatisfied	T10	U	U	U	L	L	L	U
	C	347	27	3,400 (300)	EA	0.125% bupivacaine 10 mL + 12.5 μg epinephrine.		8.4% dissatisfied	T10							
Murphy *et al.*1991[43]	F	43	26	3,420 (450)	EA	0.1% bupivacaine 10 mL + 50 μg fentanyl at 20 min intervals.	150 μg (100-200)	(0-100) (2-50)	NA	L	L	U	H	L	L	U
	C	42	26	3,250 (470)	EA	0.25% bupivacaine 5 mL with hourly intervals		(10-50)	NA							
Viscomi *et al.* 1990[44]	F	19	28	NA	EA	2% lidocaine 10 mL + 75 μg fentanyl.	357.4 μg (?-547)	NA	T10	U	L	H	L	U	U	H
	C	20	26	NA	EA	2% lidocaine 10 mL + 5 mL saline.			T10							
Jones *et al.*1989[45]	F	20	26.4	3,400 (2,400-5,100)	EA	2% lidocaine 4 mL + 0.5% bupivacaine 6 mL + fentanyl 100 μg and 0.08% bupivacaine 15 $mL \cdot hr^{-1}$ with fentanyl 37.5 $\mu g \cdot hr^{-1}$.	NA	(0-100) 20 (19)	T10	U	L	H	U	U	L	H
	C	19	25.3	3,600 (2,400-4,500)	EA	2% lidocaine 4 mL + 0.5% bupivacaine 6 mL + 2 mL saline and 0.08% bupivacaine 15 $mL \cdot hr^{-1}$.		25.2 (25.1)	T10							

Table 1 continued

Study	Comparison	*n*	Mean Age (yr)	Birth Weight (g)*	Anesth Method	Labour Analgesia Procedure	Dose of Opioids*	VAPS*	Block Level	Risk of bias R	B	A	C	F	O	Rank
Jorrot *et al.*1989[48]	S	42	28.5	NA	EA	12 mL of 0.25% plain bupivacaine with 15 mg sufentanil	NA	NA	NA	U	L	H	H	U	U	H
	F	41	29.6	NA	EA	12 mL of 0.25% plain bupivacaine with 75 mg fentanyl		NA	NA							
	C	41	30.1	NA	EA	0.25% plain bupivacaine 12 mL with saline		NA\	NA							
Van Steenberge *et al.*1987[46]	S	36	26.6	NA	EA	sufentanil 7.5 μg + 12.5 mg bupivacaine + 12.5 μg adrenaline.	NA	NA	NA	U	U	H	L	U	U	H
	C	34	28.3	NA	EA	bupivacaine 12.5 mg + 12.5 μg adrenaline.		NA	NA							
Milon *et al.*1986[49]	F	38	25.8	NA	EA	0.25% bupivacaine 8 mL + 0.1 mg fentanyl 2 mL	0.27 (0.14) mg	NA	NA	U	U	H	H	U	L	H
	C	43	25.9	NA	EA	0.25% bupivacaine 10 mL		NA	NA							

S = sufentanil; F = fentanyl; C = control; EA = epidural analgesia; CSEA = combined spinal epidural analgesia; SA = spinal analgesia; NA = data not available; R = randomization sequence generation; B = blinded method; A = allocation concealment; C = complete outcome data addressed; F = free of selective reporting; O = free of other bias; L = low risk; H = high risk; U = unclear risk; VAPS = visual analogue pain scale.*The data are described as median (range) or mean (SD)

Fig. 1 Selection process for RCTs included in the meta-analysis. RCT = randomized controlled trial

status of neonates who were systematically evaluated by NACS at 2 hours showed no difference between the two groups (MD −0.35, 95% CI: −1.70 to 1.01, $P = 0.62$). In the subgroup analysis, no significant difference was found ($P = 0.10$); however, it appeared that the NACS values were much lower after the use of opioids in the high risk of bias group. No significant heterogeneity was found among these trials ($I^2 = 0\%$, 95% CI: 0 to 79).

Neurological and Adaptive Capacity Scores at 24 hr

Six trials[15-17,22,23,40] comprising 161 women in the opioid group and 155 women in the control group compared NACS at 24 hr (Fig. 5). The overall evaluation showed that opioids did not influence the outcome of NACS at 24 hr (MD −0.45, 95% CI: −1.36 to 0.46, $P = 0.33$). In the subgroup analysis, the high risk group, but not the low and unclear risk of bias group, showed that opioids could induce lower NACS scores at 24 hr. No significant heterogeneity was found among these trials ($I^2 = 3\%$, 95% CI: 0 to 26).

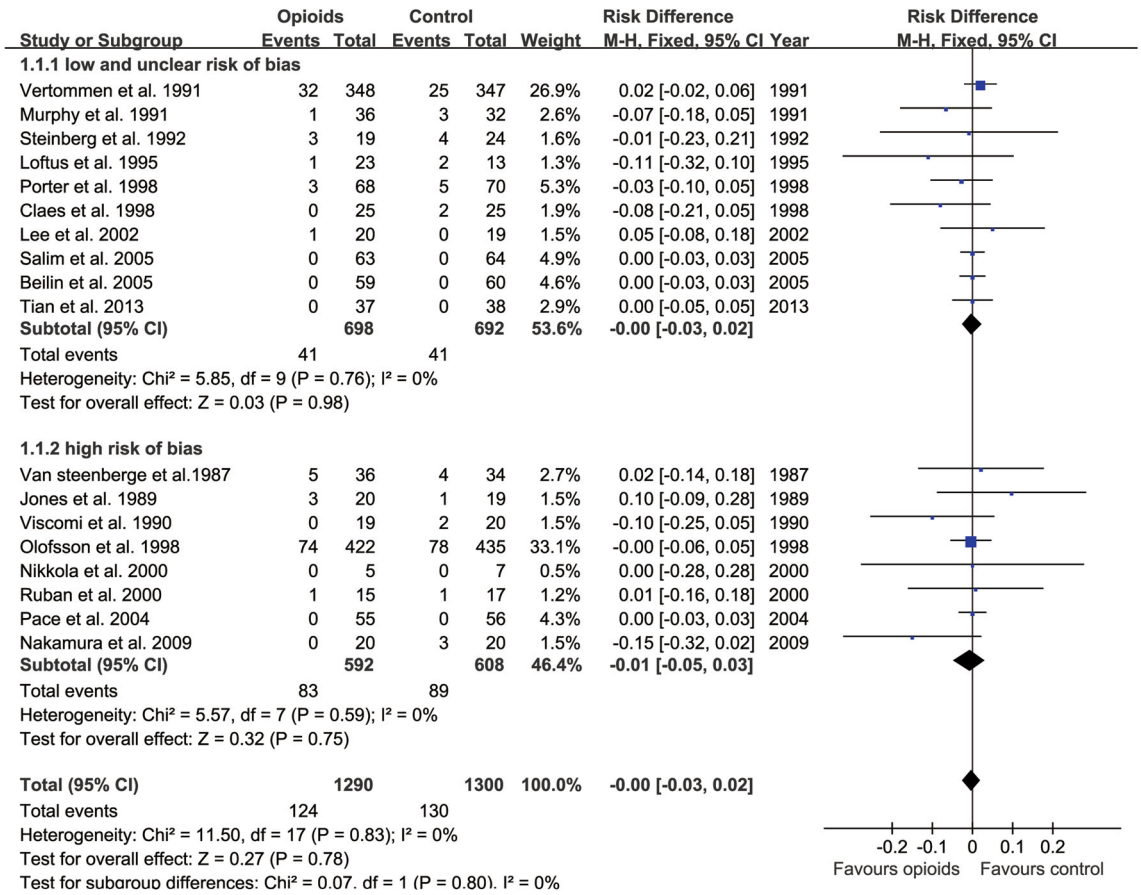

Fig. 2 The comparison of Apgar scores at one minute between the opioid and control groups. RD < 0 means that the incidence of Apgar scores < 7 is less in the opioid group compared with the control group. 95% CI = 95% confidence interval; RD = risk difference

Umbilical artery or vein pH values

Five trials[16,17,23,41,43] reported UA/UV pH values: 271 women in four trials with UA pH values and another 302 women in four trials with UV pH values. The meta-analysis indicated that opioids did not significantly alter the UA pH values (MD −0.02, 95% CI: −0.06 to 0.03, $P = 0.48$) or the UV pH values (MD −0.03, 95% CI: −0.07 to 0.00, $P = 0.08$). Obvious heterogeneity was found among these trials, indicating remaining uncertainty about the true treatment effect.

Secondary outcomes

We also performed a meta-analysis on the VAPS scores of women. Nine trials with 478 women were included to assess the efficacy of opioids in labour analgesia. Seven trials used a 0-100 scale, one trial used a 0-10 scale, and another trial used a 0-4 scale of the VAPS scoring system (Table 1); therefore, the SMD was used to assess the effects. The results indicated that additional administration of opioids was superior to the traditional method which only used local anesthetic (SMD −1.95, 95% CI: −3.06 to −0.84, $P = 0.0006$).

The potential maternal side effects, such as motor block, vomiting, pruritus, nausea, sedation, and hypotension of parturients, were also explored (Table 2). The pooled meta-analysis showed that opioids could induce significant pruritus in parturients; however, the incidence of vomiting, nausea, sedation, and hypotension was not significantly different between the opioid and control groups (Table 3). Motor block was not included in the meta-analysis; however, the individual studies[37,38,41,42] showed that opioids did not seem to affect the motor function of the women.

Sensitivity analysis and publication bias

Sensitivity analysis was performed by dividing the studies into high, low, and unclear risk of bias subgroups. Including the trials with a high risk of bias did not bias the results significantly, which meant that the evaluations in our meta-analysis were stable. The funnel plot for the

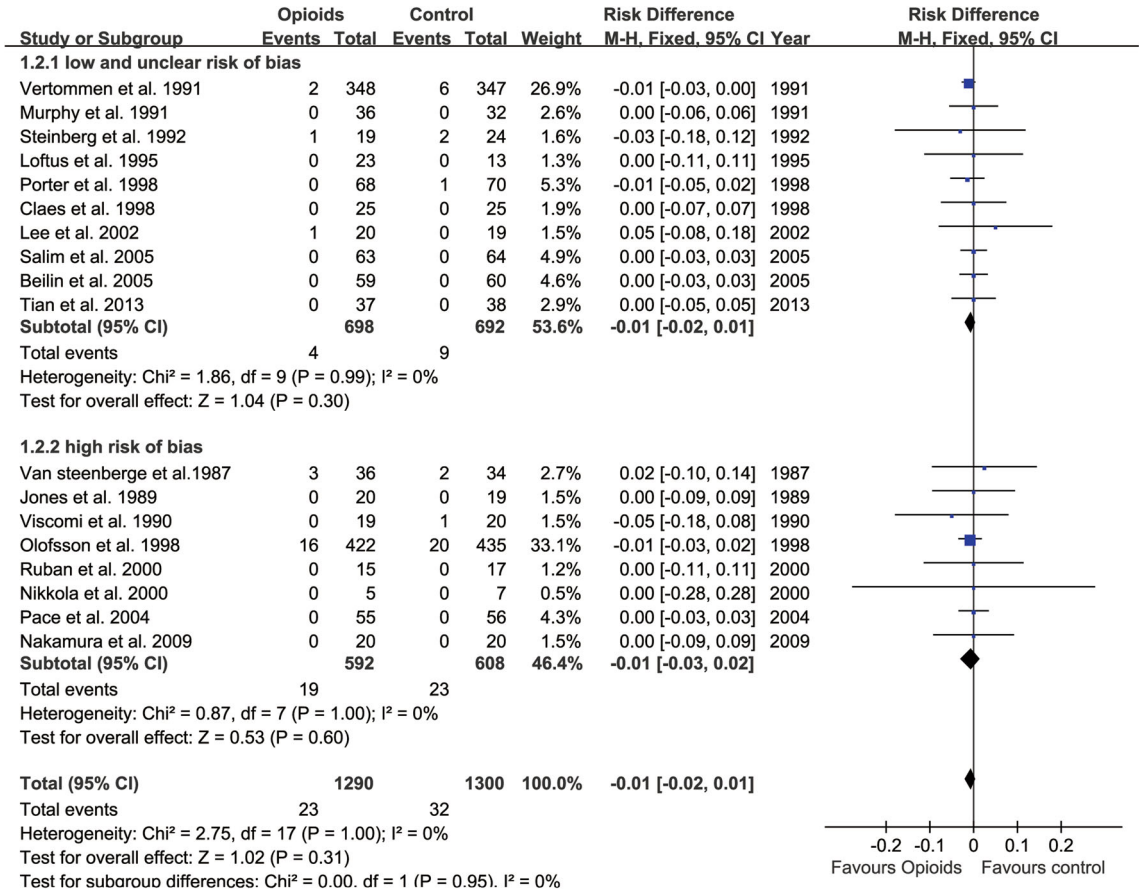

Fig. 3 The comparison of Apgar scores at five minutes between the opioid and control groups. RD < 0 means that the incidence of Apgar scores < 7 is less in the opioid group than in the control group. 95% CI = 95% confidence interval; RD = risk difference

outcome of Apgar scores at one minute was conducted and it did not reveal any asymmetry (Fig. 6).

Discussion

With labour analgesia, in addition to the efficacy of the analgesia and patient satisfaction, safety of the neonates is an important issue. In this review, we investigated the effects of epidural/spinal opioids in labour analgesia on neonatal outcomes. Twenty-one RCTs comprising 2,859 women were included in the meta-analysis.

Primary outcomes

Apgar scores are the most commonly used method to assess newborn status, and they are strong predictors of neonatal mortality.[50,51] The scoring system contains five neonatal measurements: activity (muscle tone), pulse, grimace (reflex irritability), appearance (skin colour), and respiration, which are evaluated at one minute and five minutes after birth. Neonates with Apgar scores < 7 might require resuscitative measures. In our meta-analysis, the incidence of Apgar scores < 7 was pooled to clarify whether the opioids given during labour analgesia affected the neonates. The data on Apgar scores at both one minute and five minutes were analyzed, and the results showed no difference between the two groups, which indicated that the opioids do not significantly influence the Apgar scores. The meta-analysis included only one systematic review, which described the relevant data by way of a qualitative summary and concluded that opioids did not affect Apgar scores.[29] Our meta-analysis is in agreement with this result; moreover, our review provides a more precise estimate by quantitative analysis of all data.

Neurological and Adaptive Capacity Scores is another scoring system which is more systemic and places more emphasis on neurological status. While Apgar scores may display drug-induced neurological depression, such as mild hypotonia or poor primary reflex responses,[52] the NACS was developed to differentiate drug-induced depression as a result of labour trauma, asphyxia, or neurological disease.[26] The NACS scoring system contains five aspects, including adaptive capacity, passive tone, active

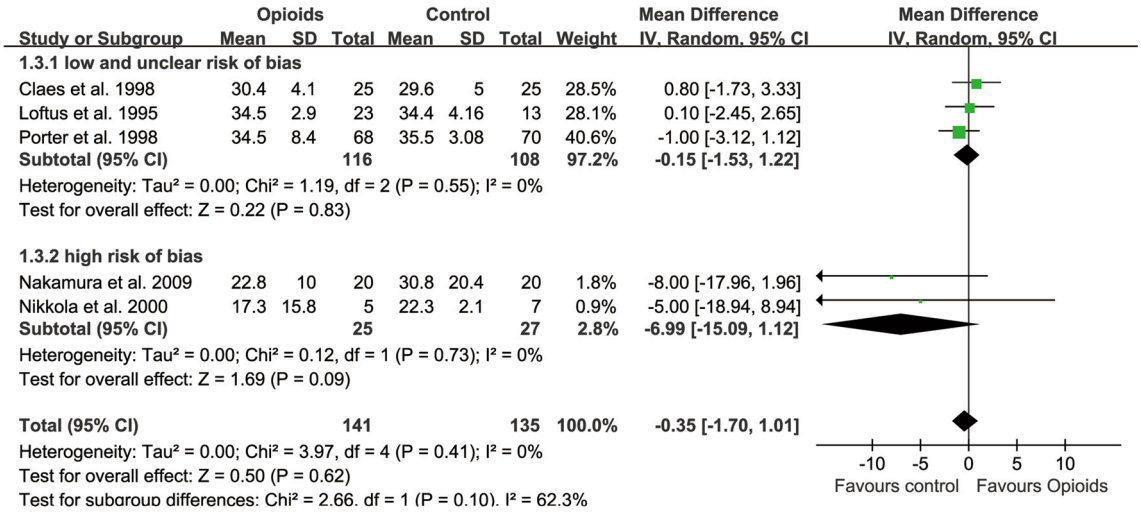

Fig. 4 The comparison of NACS at two hours after delivery between the opioid and control groups. MD < 0 means that the NACS is lower in the opioid group than in the control group. NACS = Neurological and Adaptive Capacity Scores, 95% CI = 95% confidence interval; MD = mean difference

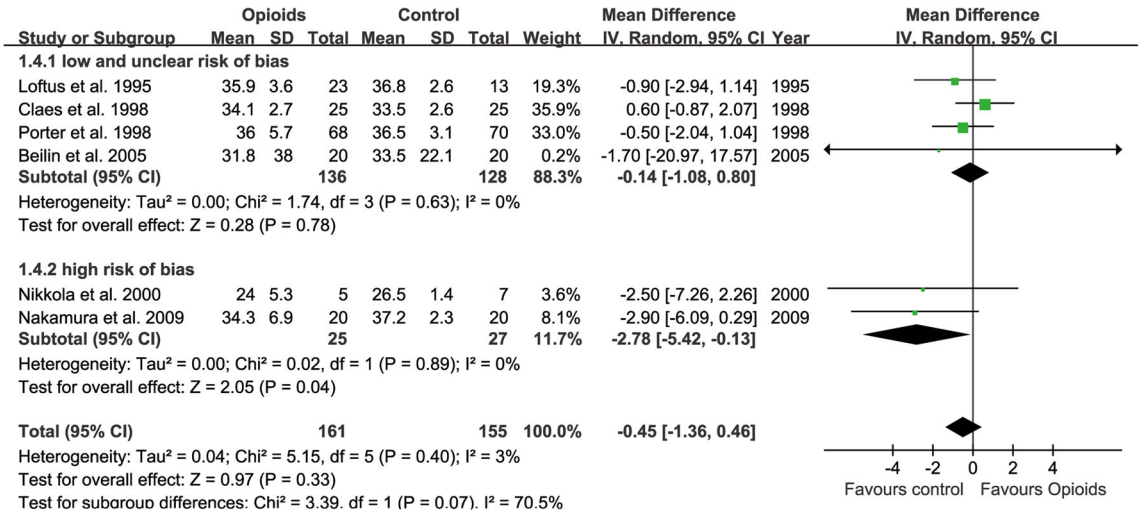

Fig. 5 The comparison of NACS at 24 hr after delivery between the opioid and control groups. MD < 0 means that the NACS is lower in the opioid group than in the control group. NACS = Neurological and Adaptive Capacity Scores, 95% CI = 95% confidence interval; MD = mean difference

tone, primary reflexes, and general neurologic status. The maximum possible total score is 40, and a score of ≥ 35 indicates a neurologically vigorous newborn. The major time points for measurement of neonatal status are two hours after delivery (short term) and 24 hr after delivery (long term); therefore, we performed the meta-analysis accordingly. The overall evaluation indicated that opioids in labour analgesia did not affect the neurological status of neonates. Two other systematic reviews focused on the NACS. One review[53] with seven RCTS compared remifentanil with meperidine for labour analgesia, and the other review[27] comprised three RCTs that assessed the effect of EA with fentanyl on neonates. Nevertheless, neither review drew an explicit conclusion regarding the NACS outcome. In our meta-analysis, we enrolled more high-quality RCTs, pooled the data, and obtained a quantitative estimation.

Umbilical artery and vein pH values are critical endpoints to determine fetal acidosis, which is a predicator of perinatal asphyxia.[54] The threshold of UA pH ranges from 7.0-7.20, while UV pH ranges from about 7.10-7.20 in most reported RCTs. A systematic review concludes that low umbilical cord pH is substantially associated with neonatal mortality and morbidity and cerebral palsy in childhood.[55] In our meta-analysis, no difference was detected between the two groups when the

Table 2 The incidence of side effects of the parturients reported in the included randomized controlled trials

	Side effects of the parturients						
	n	Motor block	Vomiting	Pruritus	Nausea	Sedation	Hypotension
Tian *et al.* 2013[13]							
S	37			4			
C	38			0			
Nakamura *et al.* 2009[15]							
S	20			7			1
C	20			0			1
Marcos *et al.* 2008[47]							
F	32		0	11	0		0
C	32		1	0	1		1
Lee *et al.* 2002[37]							
F	20	13/3/2/1	2	2	2	5	9
C	19	18/2/0/0	0	0	1	4	1
Ruban *et al.* 2000[38]							
F	15	5	3	2	3	0	0
C	17	5	0	0	0	0	2
Nikkola *et al.* 2000[23]							
F	5		0	2	2	4	
C	7		0	0	1	0	
Claes *et al.* 1998[40]							
S	25			17		1	0
C	25			1		1	0
Steinberg *et al.* 1992[41]							
S	22	1		3		0	2
C	25	9		0		0	5
Vertommen *et al.* 1991[42]							
S	344	63/36/1/0	4	26	4	8	18
C	318	42/49/9/0	4	1	5	4	20
Jones *et al.* 1989[45]							
F	20		7	15	9	0	4
C	19		4	1	6	0	2
Jorrot *et al.* 1989[48]							
S	42		4	9		6	4
F	41		3	9		4	4
C	41		3	1		3	3
Van Steenberge *et al.* 1987[46]							
S	36		5	8	7	4	
C	34		6	1	8	7	
Totals							
F	133	\	15(11.3)	41(30.8)	16(12.0)	13(9.8)	17(12.8)
S	526	\	13(2.5)	74(14.1)	11(2.1)	19(3.6)	25(4.8)
C	595	\	18(3.0)	5(0.8)	22(3.7)	19(3.2)	35(5.9)

S = sufentanil; F = fentanyl; C = control; The values in Motor block were partly presented by number of patients with Bromage score of 0/1/2/3. Bromage score was the most frequently used method to measure motor block. 0 = free movement of legs and feet; 1 = just able to flex knees with free movement of feet; 2 = unable to flex knees, but with free movement of feet; 3 = unable to move legs or feet. Totals for side effects are presented as *n* (%)

overall effects were assessed. Meanwhile, the mean values of all UA/UV pH values were above 7.23, which indicated that both the traditional and additional opioids methods did not induce significant side effects on neonates. In a meta-analysis comparing an intermittent epidural bolus with continuous epidural infusions for labour analgesia, no difference was detected in UA/UV pH values.[4] In another study, no difference was found in UA/UV pH values when remifentanil was compared with meperidine in labour analgesia.[53]

Table 3 The meta-analyses of the parturients' side effects (using a fixed-effect model)

	RCTs (*n*)	RD	95% CI for RD	*P values*	I^2	95% CI for I^2
Pruritus	12	17%	14 to 19	<0.00001	89%	82 to 93
Vomiting	6	1%	−1 to 4	0.37	17%	0 to 60
Nausea	7	1%	−2 to 4	0.48	28%	0 to 69
Sedation	9	2%	−1 to 4	0.21	57%	9 to 80
Hypotension	9	0%	−3 to 3	0.81	48%	0 to 76

RCTs = randomized controlled trials; CI = confidence interval; RD = risk difference; RD and 95% CI represented the point and interval estimate for the treatment effect; *P* values are for the test of the overall treatment effect; I^2 and 95% CI are for the point and interval estimate for the heterogeneity statistic

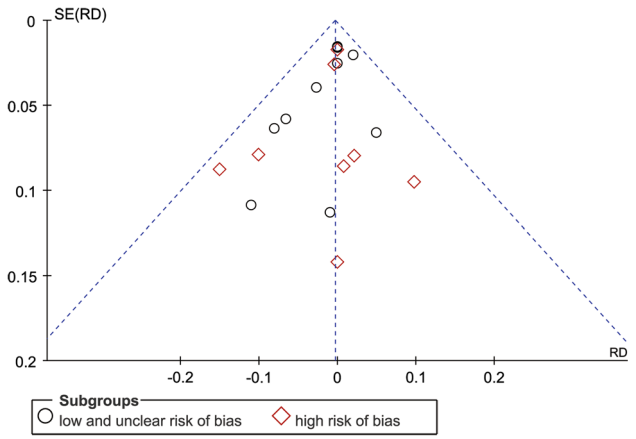

Fig. 6 Funnel plot for the outcome of Apgar scores at one minute. No obvious asymmetry was found, which indicated that no significant publication bias was detected in this meta-analysis

Secondary outcomes

Patient satisfaction and side effects, important factors in the assessment of the quality of labour analgesia, have been evaluated in other systematic reviews and meta-analyses. George *et al.* reported that administering an intermittent epidural bolus was superior to a continuous epidural infusion, as measured by the VAPS score.[4] Leong *et al.* reported that the VAPS score was higher in the remifentanil group than in the meperidine group at one hour after injection.[53] Schnabel *et al.* indicated that remifentanil was more effective than pethidine, and that remifentanil continuous EA is superior to patient-controlled analgesia.[56] In our meta-analysis, we focused on evaluating the efficacy of epidural/spinal opioids with labour analgesia and found that the addition of opioids to a local anesthetic can significantly improve the VAPS score.

The common maternal side effects induced by opioids include motor block, vomiting, pruritus, nausea, sedation, and hypotension. In our study, we displayed all of the data in the individual RCTs and performed a meta-analysis. The results indicated that opioids did not induce any side effects other than significant pruritus. In addition, the results were in agreement with other studies that focused on the side effects of opioids.[57-59] After making a trade-off between neonate and maternal outcomes, in our view, labour analgesia with opioids is worth considering, especially an epidural/spinal method.

Limitations and future directions of the study

In our meta-analysis, the methods and duration of opioid administration varied amongst the individual studies, which was probably a source of the heterogeneity. In addition, the RCTs which met the inclusion criteria concerned only fentanyl and sufentanil. Consequently, the effects of other opioids, such as remifentanil and morphine, were not included in our review. Furthermore, all outcomes were measured within 24 hr after delivery, therefore the long-term effects of opioids on neonates could not be evaluated. As previously mentioned, more well-designed RCTs should focus on these factors to add additional clarification.

In conclusion, the results of this meta-analysis showed that the commonly administered doses of fentanyl and sufentanil for labour analgesia are safe up to 24 hr after delivery. Future studies should focus on the long-term neonatal side effects.

Conflicts of interest None declared.

Appendix

The formulas used to calculate standard deviation (SD) in this meta-analysis are listed below:

(1) The formula can be used to estimate the SD from the standard error of the mean (SEM) and the sample size (*n*).

$$SD = SEM \times \sqrt{n}$$

(2) The formula can be used to estimate the mean using the median (*m*) and the low and high end of the range (a and b, respectively).[60]

$$\overline{x} \approx \frac{a + 2m + b}{4}$$

The SD (S) can be estimated by

$$S^2 \approx \frac{1}{12}\left(\frac{(a - 2m + b)^2}{4} + (b - a)^2\right)$$

(3) The formula can be used to estimate pooled SD (S) from separate SD_1 (S_1), n_1 and SD_2 (S_2), n_2 …

$$s^2 \frac{(n-1)s^2 + (n_2 - 1)s_2^2 + \cdots + (n_k - 1)s_k^2}{n_1 + n_2 + \cdots + n_k - k}$$

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