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REPORTS OF ORIGINAL INVESTIGATIONS

The effect of low concentrations *versus* high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis

L'effet de la concentration d'anesthésique local pour l'analgésie du travail obstétrical sur les pronostics obstétricaux et anesthésiques: une méta-analyse

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Abstract

Introduction *The influence that different concentrations of labour epidural local anesthetic have on assisted vaginal delivery (AVD) and many obstetric outcomes and side effects is uncertain. The purpose of this meta-analysis was to determine whether local anesthetics utilized at low concentrations (LCs) during labour are associated with a decreased incidence of AVD when compared with high concentrations (HCs).*

Methods *We searched PubMed, Ovid EMBASE, Ovid MEDLINE, CINAHL, Scopus, clinicaltrials.gov, and Cochrane databases for randomized controlled trials of labouring patients that compared LCs (defined as ≤ 0.1% epidural bupivacaine or ≤ 0.17% ropivacaine) of epidural local anesthetic with HCs for maintenance of analgesia. The primary outcome was AVD and secondary outcomes included Cesarean delivery, duration of labour, analgesia, side effects (nausea and vomiting, motor block, hypotension, pruritus, and urinary retention), and neonatal outcomes. The odds ratios (OR) or weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated using random effects modelling. An OR < 1 or a WMD < 0 favoured LCs.*

Results *Eleven studies met our criteria (eight bupivacaine and three ropivacaine studies), providing 1,145 patients in the LCs group and 852 patients in the HCs group for analysis of the primary outcome. Low concentrations were associated with a reduction in the incidence of AVD (OR = 0.70; 95% CI 0.56 to 0.86; P < 0.001). There was no difference in the incidence of Cesarean delivery (OR 1.05; 95% CI 0.82 to 1.33; P = 0.7). The LCs group had less motor block (OR 3.9; 95% CI 1.59 to 9.55; P = 0.003), greater ambulation (OR 2.8; 95% CI 1.1 to 7.14; P = 0.03), less urinary retention (OR 0.42; 95% CI 0.23 to 0.73; P = 0.002), and a shorter second stage of labour (WMD −14.03; 95% CI −27.52 to −0.55; P = 0.04) compared with the HCs group. There were no differences between groups in pain scores, maternal nausea and vomiting, hypotension, fetal heart rate abnormalities, five-minute Apgar scores, and need for neonatal resuscitation. One-minute Apgar scores < 7 favoured the HCs group (OR 1.53; 95% CI 1.07 to 2.21; P = 0.02), and there was more pruritus in the LCs group (OR 3.36; 95% CI 1.00 to 11.31; P = 0.05).*

Conclusion *When compared with HCs of local anesthetics, the use of LCs for labour epidural analgesia reduces the incidence of AVD. This may be due to a*

Author contributions *Pervez Sultan*, *Caitriona Murphy*, *Stephen Halpern*, and *Brendan Carvalho* made substantial contributions to the conception and design of the study and were involved in drafting the article for important intellectual content.

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reduction in the amount of local anesthetic used and the subsequent decrease in motor blockade. We therefore recommend the use of LCs of local anesthetics for epidural analgesia to optimize obstetric outcome.

Résumé

Objectif *Nous connaissons mal l'influence de différentes concentrations d'anesthésique local pour la péridurale du travail obstétrical sur l'accouchement vaginal assisté (AVA) ainsi que sur de nombreux pronostics obstétricaux et effets secondaires. L'objectif de cette méta-analyse était de déterminer si les anesthésiques locaux utilisés à de faibles concentrations (FC) pendant le travail obstétrical étaient associés à une incidence réduite d'AVA par rapport à des concentrations élevées (CE).*

Méthode *Nous avons fait des recherches dans les bases de données PubMed, Ovid EMBASE, Ovid MEDLINE, CINAHL, Scopus, clinicaltrials.gov et Cochrane pour en tirer les études randomisées contrôlées portant sur des patientes en travail obstétrical et comparant des FC (définies comme étant ≤ 0,1 % de bupivacaïne ou ≤ 0,17 % de ropivacaïne en péridurale) d'anesthésique local péridural à des CE pour le maintien de l'analgésie. Le critère d'évaluation principal était l'AVA, et les critères secondaires comprenaient l'accouchement par césarienne, la durée du travail obstétrical, l'analgésie, les effets secondaires (nausées et vomissements, bloc moteur, hypotension, prurit et rétention urinaire), et l'état du nouveau-né. Les rapports de cotes (RC) ou différences moyennes pondérées (DMP) et les intervalles de confiance (IC) à 95 % ont été calculés à l'aide d'un modèle à effets aléatoires. Un RC < 1 ou une DMP < 0 ont été considérés comme favorisant les FC.*

Résultats *Onze études respectaient nos critères de sélection (huit études sur la bupivacaïne et trois sur la ropivacaïne), donnant un total de 1145 patientes dans le groupe FC et de 852 patientes dans le groupe CE pour l'analyse de notre critère d'évaluation principal. Les faibles concentrations ont été associées à une réduction de l'incidence d'AVA (RC = 0,70; IC 95 % 0,56 à 0,86; P < 0,001). Aucune différence dans l'incidence d'accouchement par césarienne n'a été observée (RC 1,05; IC 95 % 0,82 à 1,33; P = 0,7). Dans le groupe FC, on a observé une incidence moindre de blocs moteurs (RC 3,9; IC 95 % 1,59 à 9,55; P = 0.003), une meilleure ambulation (RC 2,8; IC 95 % 1,1 à 7,14; P = 0,03), une rétention urinaire moindre (RC 0,42; IC 95 % 0,23 à 0,73; P = 0,002) et un deuxième stade de travail obstétrical plus court (DMP −14,03; IC 95 % −27,52 à −0,55; P = 0,04) que dans le groupe CE. Aucune différence n'a été observée entre les groupes en matière de scores de douleur, de nausées et vomissements maternels, d'hypotension, d'anomalies de la fréquence cardiaque fœtale, de scores Apgar à cinq minutes, et de besoin de réanimation néonatale. Les scores Apgar < 7 à une minute se retrouvaient davantage dans le groupe CE (RC 1.53; IC 95 % 1.07 à 2.21; P = 0.02), et on a observé plus de prurit dans le groupe FC (RC 3,36; IC 95 % 1,00 à 11,31; P = 0,05).*

Conclusion *Par rapport à des CE d'anesthésiques locaux, l'utilisation de FC pour l'analgésie péridurale du travail obstétrical réduit l'incidence d'AVA. Cela pourrait être lié à une réduction de la quantité d'anesthésique local utilisée et à la réduction subséquente du bloc moteur. C'est pourquoi nous recommandons l'utilisation de FC d'anesthésiques locaux pour l'analgésie péridurale pour optimiser le pronostic obstétrical.*

Epidural drug administration is regarded as the gold standard for labour analgesia, resulting in improved pain and maternal satisfaction scores when compared with other techniques.[1–4] Nevertheless, labour epidural analgesia may be associated with side effects, including prolonged labour, increased incidence of assisted vaginal delivery (AVD),[4,5] reduced ability to ambulate,[6] pruritus,[7] hypotension,[8] requirement for urinary catheterization,[9] and abnormal fetal heart rate.[10] Limiting the dose of local anesthetic and use of adjuvant drugs, such as opioids and epinephrine, may potentially reduce these side effects.

The Comparative Obstetric Mobile Epidural Trial (COMET) showed a reduced AVD rate with a low-dose epidural infusion (0.1% bupivacaine) when compared with a higher dose (0.25% bupivacaine).[5] In contrast to the COMET study, a number of other studies have shown no difference in AVD.[11–14] These studies differed in the local anesthetic utilized, the concentrations of local anesthetic solution, or the varying combinations of bolus and/or continuous background infusion rates. Although the COMET study showed that the concentration of local anesthetic had an effect on AVD in nulliparous women, it was performed in only two tertiary delivery centres within the U.K., which may limit the broad generalizability of their findings to other obstetric populations and practices within and outside the U.K. A recent review by Loubert *et al.* highlighted the need for further studies to elucidate the impact of epidural solutions and regimens on outcomes such as the rate of AVD and the duration of labour.[15]

The primary aim of this meta-analysis was to investigate whether labour epidural local anesthetic regimens utilizing low concentrations (LCs) (≤ 0.1% bupivacaine or an equivalent ropivacaine concentration) decrease the incidence of AVD (ventouse or forceps-assisted vaginal delivery) when compared with higher concentrations (HCs) of

local anesthetic without compromising analgesia. Secondary outcomes included obstetric outcomes, maternal outcomes, maternal side effects, and neonatal outcomes.

Methods

For this meta-analysis, we sought randomized controlled trials comparing LCs of local anesthetics with HCs for maintenance of epidural analgesia in labouring women. Low concentrations were defined as $\leq 0.1\%$ bupivacaine or an equipotent concentration of ropivacaine ($\leq 0.17\%$).[16,17] There is no universally accepted concentration that is regarded as a low concentration. We decided to use $> 0.1\%$ bupivacaine as our cut-off value for high concentration because this value is utilized in many randomized controlled studies, including the largest trial (COMET) to represent HCs of epidural solution.

We conducted a literature search with no language restriction on August 20, 2011 and repeated the search on February 6, 2012. Searches were performed in PubMed (1950 to February 2012), Ovid EMBASE (1970 to August 2011), Ovid MEDLINE (1950 to August 2011), Scopus (1960 to February 2012), EBM Reviews Cochrane Central Register of Controlled Trials 2nd Quarter 2011, clinicaltrials.gov, and CINAHL (August 2011). Finally, we attempted to reduce publication bias by consulting the clinical trials registry (www.clinicaltrials.gov) on April 23, 2012. The search strategy consisted of a combination of subject headings (*obstetric, labour, epidural*) and keywords/key phrases (*bupivacaine, ropivacaine, labour, delivery, birth and trial*) for each of MEDLINE, EMBASE, and CINAHL searched in specified fields (such as *ti = title/ab = abstract*). In the event that a database did not index articles, we conducted keyword searching in the entire record (see Appendix 1 for detailed PubMed search criteria; other search strategies are available from the authors).

Reference lists of all identified studies were checked as well as those of previous meta-analyses on the same topic. All neuraxial techniques used to initiate the block (combined spinal-epidural (CSE), epidural) and different methods of administration (patient-controlled epidural analgesia, continuous epidural infusion, and clinician epidural top-ups) were considered. We included studies comparing groups that consistently utilized either LCs or HCs of epidural local anesthetics to establish and maintain labour analgesia, and we included studies with variations in opioid use between groups. Studies were excluded if they utilized epinephrine, administered HCs of local anesthetic to initiate analgesia and maintained analgesia with LCs of local anesthetics, or did not evaluate outcomes related to maintenance of labour analgesia with an epidural regimen. We did not exclude studies that used HCs of local anesthetics for rescue analgesia. Attempts were made to contact the original authors for additional data when required.

The quality of studies included in the meta-analysis was reviewed using the Cochrane Collaboration's tool for assessing risk of bias.[18] Areas of methodological quality assessed included concealment of allocation, random sequence generation, blinding of the assessors and participants, and accounting for all subjects. We did not assess reporting bias (selective reporting of outcomes). Overall quality was graded as low (low risk of bias), high (high risk of bias), or unclear risk of bias for each domain entry using a standardized tool.[18] At least two individuals extracted the study data independently utilizing a standardized review protocol and recorded the information on a data collection sheet (Appendix 2). Differences were resolved by re-examination of the original manuscripts and by discussion. The data were then entered into a computer by one of the authors (C.M.) and checked by a second investigator (P.S.).

The primary outcome was the incidence of AVD. Secondary outcomes included 1) obstetric outcomes (incidence of spontaneous vaginal delivery [SVD], rate of Cesarean delivery, duration of first and second stages of labour); 2) maternal outcomes (analgesia - worst pain score measured from 0-100 after three hours of epidural infusion), total dose of epidural local anesthetic utilized, number of interventions required by the anesthesia care providers, maternal satisfaction scores, no motor block (Bromage scores $= 0$), and maternal ambulation during labour; 3) maternal side effects (nausea and vomiting, hypotension, pruritus, and urinary retention); and 4) neonatal outcomes (Apgar scores > 7 at one and five minutes, fetal heart rate, umbilical cord blood gas values, and requirement for neonatal resuscitation).

Data were analyzed using Review Manager 5.1 (Review Manager (RevMan) Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).[19] For dichotomous outcomes, the odds ratio (OR) and 95% confidence interval (CI) were calculated (an $OR < 1$ favoured LCs). The risk difference and number needed to treat were calculated for the primary outcome. In addition, risk difference and number needed to harm were calculated for dichotomous side effects. For continuous data, the weighted mean difference (WMD) and 95% CI were determined. The percentage of heterogeneity was assessed with the I^2 statistic. A P value < 0.05 was considered statistically significant. All data were combined and analyzed using the DerSimonian-Laird random effects model.

Results

The flow diagram of the study selection is provided in Fig. 1. Fifteen articles met our inclusion criteria (12 bupivacaine

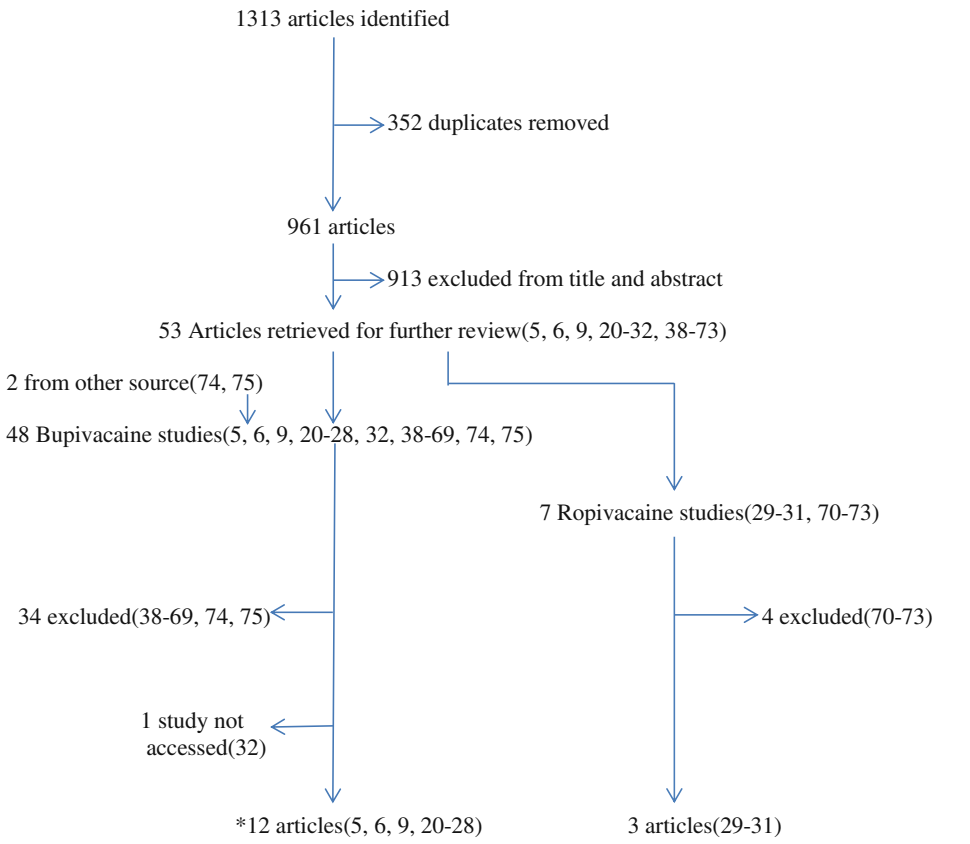

Fig. 1 Flow diagram outlining meta-analysis search

*5 publications from COMET trial grouped as 1 study(5, 6, 9, 20, 21) (therefore 8 bupivacaine studies)

11 studies met the inclusion criteria (8 bupivacaine and 3 ropivacaine)

articles[5,6,9,20–28] and three ropivacaine articles).[29–31] The five publications from the COMET study group were presented as one study.[5,6,9,20,21] One manuscript was not available and was therefore excluded.[32] Consequently, 15 articles (11 studies) involving 1,145 patients in the LCs group and 852 patients in the HCs group were analyzed for our primary outcome. The study demographics and risk-of-bias assessments are shown in the Table and Fig. 2. Excluded studies are listed in Appendix 3.

Assisted vaginal delivery

Eleven studies recorded assisted vaginal delivery as an outcome. Figure 3 shows the combined data for this outcome. Assisted vaginal delivery was reduced in the LCs group with a pooled OR of 0.70 (95% CI 0.56 to 0.86; $P < 0.001$). There was negligible heterogeneity ($I^2 = 0\%$; $P = 0.47$). The pooled risk difference was −0.07 (95% CI −0.11 to −0.04; $P < 0.001$) yielding a number needed to treat of 14 (95% CI 9 to 25).

Other obstetric outcomes

Obstetric outcomes are summarized in Fig. 4. The duration of the second stage of labour favoured the LCs group (WMD −14.03; 95% CI −27.52 to −0.55; $P = 0.04$). There was no difference in the incidence of Cesarean delivery or first stage labour between the groups (Fig. 4).

Maternal outcomes and side effects

Maternal outcomes are summarized in Fig. 5, and maternal side effects are presented in Fig. 6. Labour pain (defined as worst pain score as measured by a visual or verbal analogue scale of 0 to 100) after three hours of epidural insertion was not different between groups (WMD −0.71; 95% CI −6.30 to 4.89; $P = 0.80$). It is noteworthy that the COMET study[5] could not be included in this outcome because the authors did not report a measure of dispersion. The total dose of local anesthetic administered was lower in the LCs group (WMD −27.00; 95% CI −35.22 to

Table Study demographics and characteristics

Author Year (Reference)	Population	Low Concentrations (LCs)			High Concentrations (HCs)			Mode of Maintenance and Author Comments
		N	Drug -Test dose -Additive -Initial - Maintenance	Concentrations, Bolus Size and Rate	N	Drug -Test dose -Additive -Initial -Maintenance	Concentrations, Bolus Size and Rate	
Atienzar 2004([29])	Nulliparous	38	-No test dose -Fentanyl -Ropivacaine + Fentanyl -Ropivacaine + Fentanyl	-N/A -2 $\mu g \cdot mL^{-1}$ -0.2% 9 mL + 50 μg -0.1% + 2 $\mu g \cdot mL^{-1}$ @10 $mL \cdot hr^{-1}$	39	-No test dose -Fentanyl -Ropivacaine + Fentanyl -Ropivacaine + Fentanyl	-N/A -2 $\mu g \cdot mL^{-1}$ -0.2% 9 mL + 50 μg -0.2% + 2 $\mu g \cdot mL^{-1}$ @ 8 $mL \cdot hr^{-1}$	CEI LCs group rate of infusion is 10 $mL \cdot hr^{-1}$ *vs* 8 $mL \cdot hr^{-1}$ in HCs group.
Benhamou 2002([23])	Mixed parity	35	-No test dose -Sufentanil -Bupivacaine + Sufentanil -Bupivacaine + Sufentanil	-N/A -0.25 $\mu g \cdot mL^{-1}$ -0.0625% + 0.25 $\mu g \cdot mL^{-1}$ 3-5 mL bolus (total 10-15 mL) -0.0625% 3-5 mL + 0.25 $\mu g \cdot mL^{-1}$ @ 10-15 $mL \cdot hr^{-1}$	23	-No test dose -No additive -Bupivacaine -Bupivacaine	-N/A -N/A -0.125% 3-5 mL bolus (total 10-15 mL) -0.125% @ 15 $mL \cdot hr^{-1}$	CEI Opioid additive in LCs group only. Singleton breech labouring parturients.
COMET Study Group UK -COMET 2001([5]) -COMET 2002([21]) -Wilson 2009([6]) -Wilson 2009([9]) -Cooper 2010([20])	Mixed parity	701	-No test dose -Fentanyl -Bupivacaine + Fentanyl -Bupivacaine + Fentanyl	-N/A -2 $\mu g \cdot mL^{-1}$ -0.25% 1 mL + 25 μg (CSE: IT) -0.1% + 2 $\mu g \cdot mL^{-1}$ 15 mL (CSE group 1st bolus + CEI group) -0.1% + 2 $\mu g \cdot mL^{-1}$ 10 mL (CSE group: max 1 bolus/30 min) -0.1% + 2 $\mu g \cdot mL^{-1}$ 10 ml/hr (CEI group)	353	-Lidocaine -No additive -Bupivacaine -Bupivacaine	-2% 3 mL -N/A -0.25% 10 mL -0.25% 10 mL (max 1 $bolus \cdot hr^{-1}$)	LCs subgroups (2): 1. CEI 2. CSE + intermittent epidural bolus on maternal request HCs group: intermittent epidural bolus on maternal request. Opioid additive in LCs group only.
Dahl 1999([22])	Mixed parity	46	-Bupivacaine + Sufentanil -Sufentanil -Bupivacaine + Sufentanil -Bupivacaine + Sufentanil	-0.0625% + 1 $\mu g \cdot mL^{-1}$ 5 mL -1 $\mu g \cdot mL^{-1}$ -0.0625% + 1 $\mu g \cdot mL^{-1}$ 5 mL -0.0625% + 1 $\mu g \cdot mL^{-1}$ @ 5 $mL \cdot hr^{-1}$	45	-Bupivacaine -No additive -Bupivacaine -Bupivacaine	-0.25% 5 mL -N/A -0.25% 5 mL -0.25% @ 5 $mL \cdot hr^{-1}$	CEI Opioid additive in LCs group only. Group receiving 0.0625% bupivacaine + sufentanil 1 $\mu g \cdot mL^{-1}$ + epinephrine 1 $\mu g \cdot mL^{-1}$ excluded from analysis.

Table continued

Author Year (Reference)	Population	Low Concentrations (LCs)			High Concentrations (HCs)			Mode of Maintenance and Author Comments
		N	Drug -Test dose -Additive -Initial - Maintenance	Concentrations, Bolus Size and Rate	N	Drug -Test dose -Additive -Initial -Maintenance	Concentrations, Bolus Size and Rate	
Ginosar 2010([24])	Nulliparous	43	-No test dose -Fentanyl -Bupivacaine + Fentanyl -Bupivacaine	-N/A -1 $\mu g \cdot kg^{-1}$ -0.0625% + 1 $\mu g \cdot kg^{-1}$ 20 mL -0.0625% PCEA 20 $mL \cdot hr^{-1}$, bolus 10 mL, lockout 15 min	24	-No test dose -Fentanyl -Bupivacaine + Fentanyl -Bupivacaine	-N/A -1 $\mu g \cdot kg^{-1}$ -0.25% + 1 $\mu g \cdot kg^{-1}$ 5 mL -0.25% PCEA 5 $mL \cdot hr^{-1}$, bolus 2.5 mL, lockout 15 min	PCEA. Both groups contained opioid additive in the loading dose only.
Gogarten 2004([31])	Mixed parity	103	-No test dose -Sufentanil -Ropivacaine + Sufentanil -Ropivacaine + Sufentanil	-N/A -0.75 $\mu g \cdot mL^{-1}$ -0.125% + 0.75 $\mu g \cdot mL^{-1}$ 10 mL -0.125% + 0.75 $\mu g \cdot mL^{-1}$ bolus 4 mL, lockout 15 min	206	-No test dose -Sufentanil -Ropivacaine + Sufentanil or Ropivacaine only -Ropivacaine + Sufentanil or Ropivacaine only	-N/A -0.75 $\mu g \cdot mL^{-1}$ -0.175% + 0.75 $\mu g \cdot mL^{-1}$ 10 mL or 0.2% 10 mL -0.175% + 0.75 $\mu g \cdot mL^{-1}$ or 0.2% bolus 4 mL, lockout 15 min	PCEA Group receiving bupivacaine 0.125% + sufentanil 0.75 $\mu g \cdot mL^{-1}$ was excluded from analysis. HCs group combined 2 groups of differing concentrations: 0.2% group omitted sufentanil additive.
James 1998([26])	?Mixed parity	35	-No test dose -Fentanyl -Bupivacaine + Fentanyl -Bupivacaine + Fentanyl	-N/A -2 $\mu g \cdot mL^{-1}$ -0.1% 15 mL + 50 µg -0.1% + 2 $\mu g \cdot mL^{-1}$ 10 mL bolus prn	38	-No test dose -No additive -Bupivacaine -Bupivacaine	-N/A -N/A -0.25% 15 mL -0.25% 10 mL prn	Intermittent epidural bolus LCs and HCs groups. Unclear parity of the study population.
Khan 2004([25])	Mixed parity	25	-Lidocaine -Fentanyl -Bupivacaine + Fentanyl -Bupivacaine + Fentanyl	-2% 3 mL with epinephrine -1 $\mu g \cdot mL^{-1}$ -0.0625% 10 mL + 1 $\mu g \cdot mL^{-1}$ -0.0625% 10 mL + 1 $\mu g \cdot mL^{-1}$ @ 8 $mL \cdot hr^{-1}$	25	-Lidocaine -No Additive -Bupivacaine -Bupivacaine	-2% 3 mL with epinephrine -N/A -0.125% 10 mL -0.125% @ 8 $mL \cdot hr^{-1}$	CEI Opioid additive in LCs group only. Infusion discontinued at full cervical dilatation.
Kumar 2009([27])	Nulliparous	30	-Bupivacaine + Fentanyl + epinephrine -Fentanyl -Fentanyl Bupivacaine + Fentanyl -Bupivacaine +Fentanyl	-0.0625% + 2 $\mu g \cdot mL^{-1}$ + 5 $\mu g \cdot mL^{-1}$ 3 mL -2 $\mu g \cdot mL^{-1}$ -25 µg IT (CSE) 0.0625% + 2 $\mu g \cdot mL^{-1}$ 10 mL (Epi) -0.0625% + 2 $\mu g \cdot mL^{-1}$ 10 mL prn	30	Bupivacaine + Fentanyl + epinephrine -Fentanyl -Fentanyl Bupivacaine + Fentanyl -Bupivacaine +Fentanyl	-0.125% + 2 $\mu g \cdot mL^{-1}$ + 5 $\mu g \cdot mL^{-1}$ 3 mL -2 $\mu g \cdot mL^{-1}$ -25 µg IT (CSE) 0.125% + 2 $\mu g \cdot mL^{-1}$ 10 mL (Epi) -0.0625% + 2 $\mu g \cdot mL^{-1}$ 10 mL prn	CSE followed by intermittent epidural bolus analgesia in LCs and HCs groups.

Table continued

Author Year (Reference)	Population	Low Concentrations (LCs)			High Concentrations (HCs)			Mode of Maintenance and Author Comments
		N	Drug -Test dose -Additive -Initial - Maintenance	Concentrations, Bolus Size and Rate	N	Drug -Test dose -Additive -Initial -Maintenance	Concentrations, Bolus Size and Rate	
Lee B 2002([30])	Nulliparous	39	-No test dose -Fentanyl vs. no additive -Ropivacaine -Ropivacaine	-N/A -2 $\mu g \cdot mL^{-1}$ -0.2% 10 mL -0.1% @ 10 $mL \cdot hr^{-1}$	19	-No test dose -No additive -Ropivacaine -Ropivacaine	-N/A -N/A -0.2% 10 mL -0.2% @ 10 $mL \cdot hr^{-1}$	CEI LCs group 0.1% ropivacaine combined subgroups with ($n = 20$) and without ($n = 19$) Fentanyl additive.
Narayanan 2009([28])	Mixed parity	50	-No test dose -Sufentanil -Bupivacaine + Sufentanil -Bupivacaine + Sufentanil	-N/A -20 µg -0.0625% + 20 µg 10 mL -0.0625% + 20 µg ?volume	50	-No test dose -Sufentanil -Bupivacaine + Sufentanil -Bupivacaine + Sufentanil	-N/A -20 µg -0.125% + 20 µg 10 mL -0.125% + 20 µg ?volume	Epidural bolus in LCs and HCs group. Error in sufentanil dose printed (mg *vs* µg).

IT = intrathecal; CSE = combined spinal-epidural; PCEA = patient-controlled epidural analgesia; N/A = not available; CEI = continuous epidural infusion

Fig. 2 Risk of bias

−18.78; $P < 0.001$), while there were no differences in the number of patients requiring clinician top-ups (OR 1.08; 95% CI 0.83 to 1.39; $P = 0.58$). The incidence of no motor block (Bromage score = 0) was higher in the LCs group (OR 3.90; 95% CI 1.59 to 9.55; $P = 0.003$), and the ability to ambulate favoured the LCs group (OR 2.80; 95% CI 1.10 to 7.14; $P = 0.03$). There was a trend towards more pruritus in the LCs group (OR 3.36; 95% CI 1.00 to 11.31; $P = 0.05$). Urinary retention was lower in the LCs group (OR 0.42; 95% CI 0.23 to 0.73; $P = 0.002$); however, the risk difference did not differ (RD −0.13; 95% CI −0.28 to 0.02; $P = 0.09$).

Fetal outcomes

Neonatal outcomes are summarized in Fig. 7. The odds of an Apgar < 7 at one minute were greater in those receiving LC epidurals (Apgar at one minute OR 1.53; 95% CI .07 to 2.21; $P = 0.02$). The Apgar > 7 at five minutes (OR 2.67;

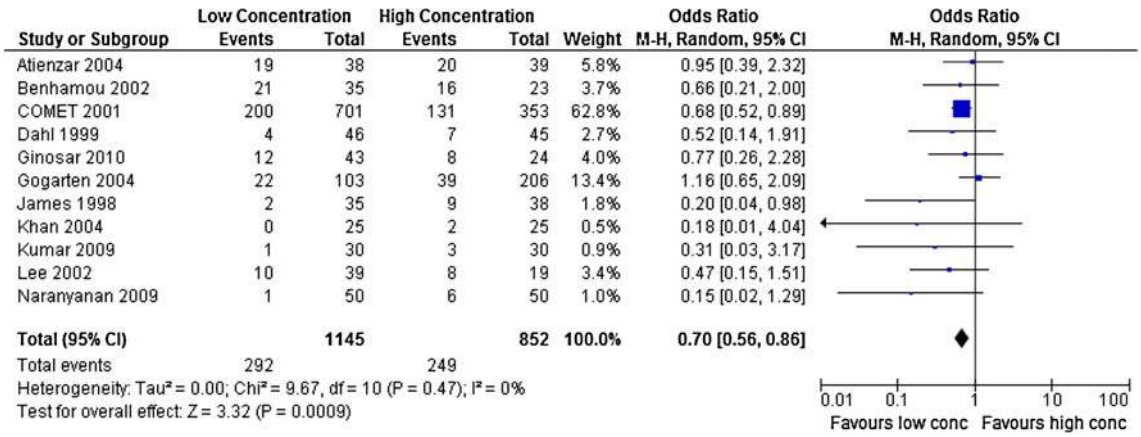

Fig. 3 Forest plot for the incidence of the primary outcome of assisted vaginal delivery (AVD)

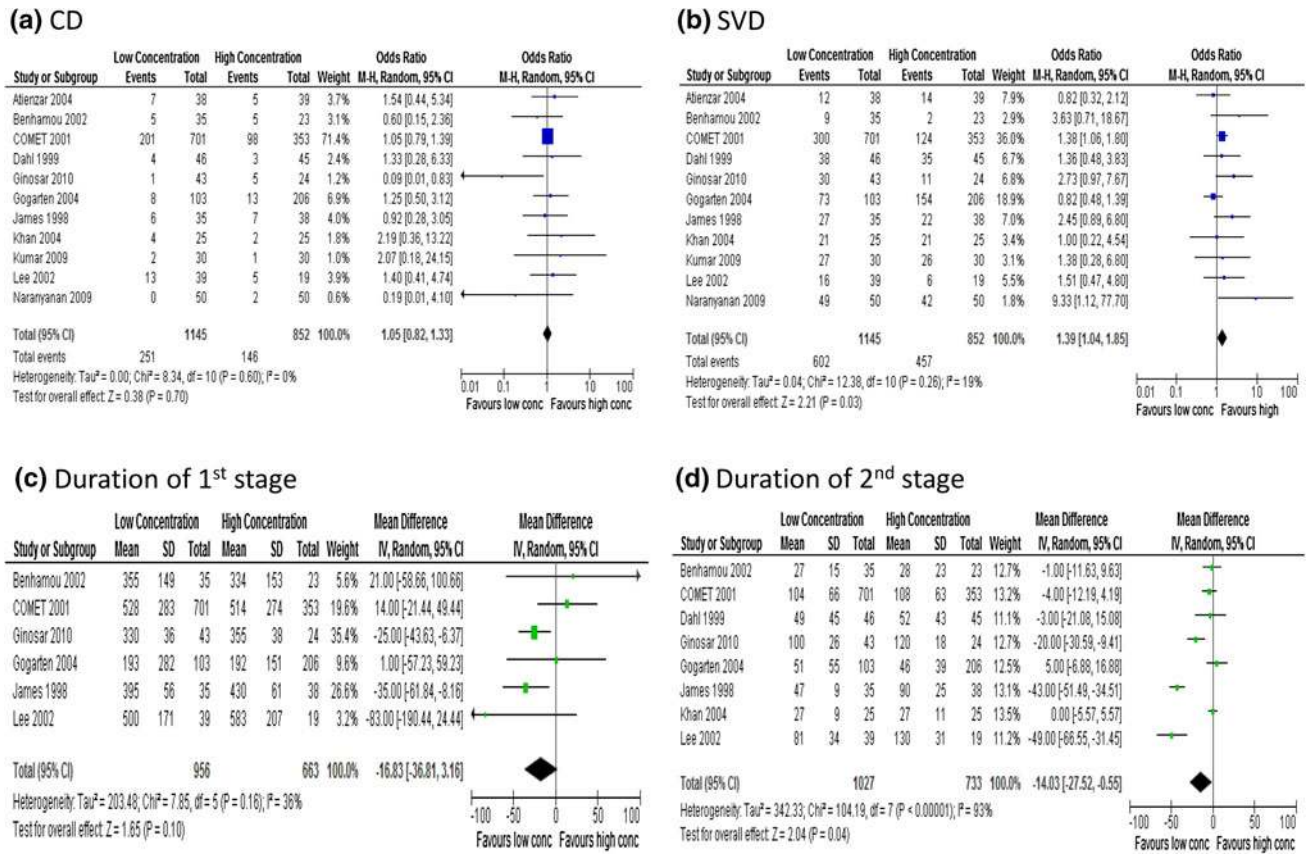

Fig. 4 Forest plots for obstetric outcomes of the incidence of A) Cesarean delivery (CD), B) spontaneous vaginal delivery (SVD), C) duration of first and D) second stages of labour (min)

95% CI 0.84 to 8.47; $P = 0.09$) and other neonatal outcomes did not differ between groups (Fig. 7).

Discussion

This meta-analysis evaluating 11 studies provides strong evidence to support the use of LCs of bupivacaine ($\leq 0.1\%$) or ropivacaine ($\leq 0.17\%$) to bring about a significant reduction in the rate of AVD. By using LCs of local anesthetic solution for epidural analgesia, 14 patients would need to be treated to prevent one additional AVD. The higher AVD rate associated with HCs of local anesthetics may be attributed to the increase in motor nerve blockade that subsequently impairs the Ferguson–Harris reflex initiating the urge to bear down.[10] Our findings showing the use of

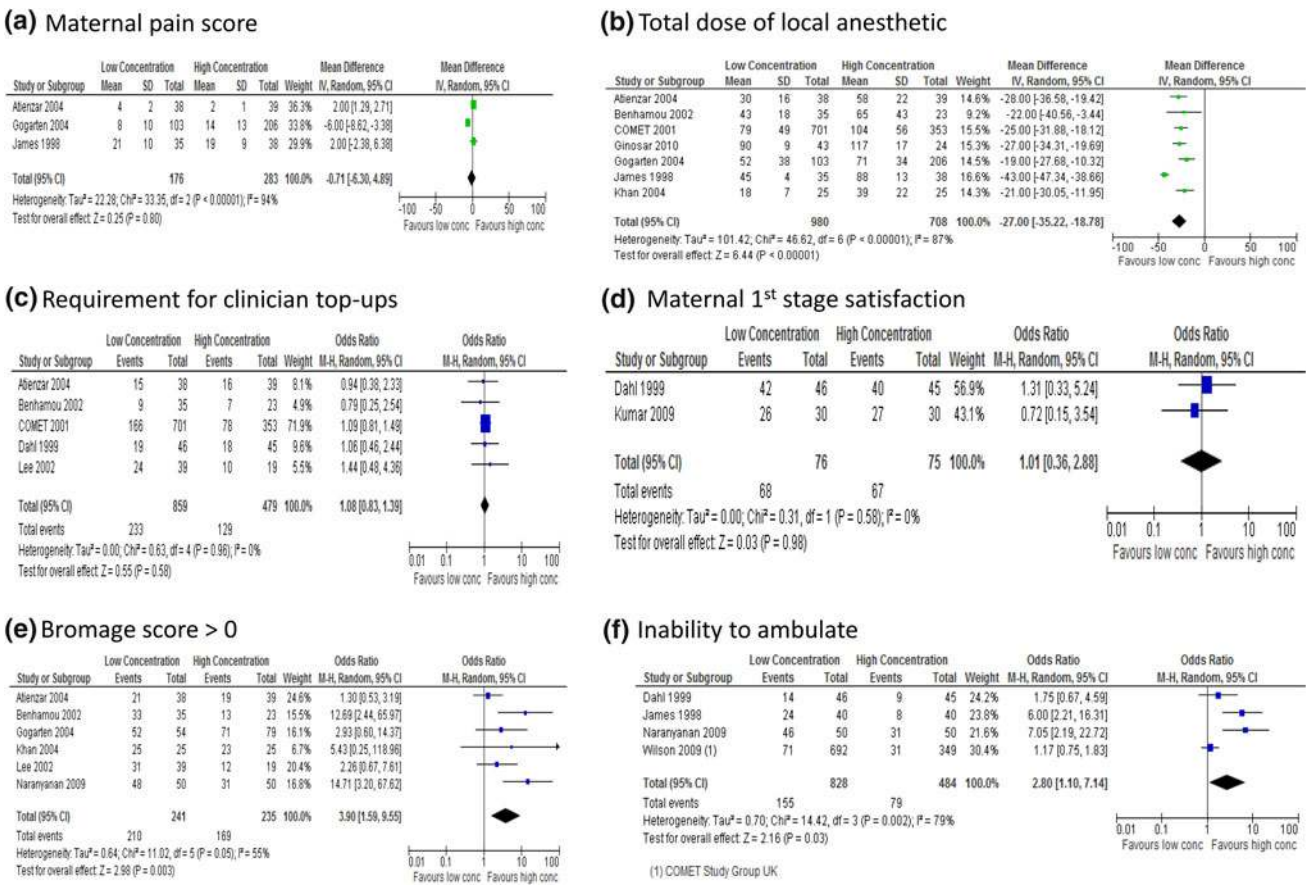

Fig. 5 Forest plots for maternal outcomes of A) pain score (visual or verbal analogue scale [VAS] 0-100 at 3 hours following neuraxial blockade placement), B) total dose of LA (mg), C) requirement of clinician top-ups, D) maternal first stage satisfaction (n/N), E) Bromage score > 0, and F) inability to ambulate

significantly decreased dosages of local anesthetic and less motor blockade in the LCs group are consistent with this explanation.

Results of the 2001 COMET study showed a lower incidence of AVD with a 0.1% bupivacaine solution than with a 0.25% concentrations.[5] Nevertheless, results from this study alone should be interpreted with caution due to numerous confounding factors, such as different methods of initiating analgesia (CSE *vs* epidural technique), initial doses, maintenance techniques (continuous infusion or intermittent bolus), drug concentrations, and group size. The three groups of patients in this study received different epidural induction and maintenance techniques. One group received an initial spinal dose of bupivacaine through a CSE technique followed by intermittent boluses on maternal request. Another group received an initial epidural dose followed by continuous infusion of the same local anesthetic mixture containing 0.1% bupivacaine and fentanyl 2 $\mu g \cdot mL^{-1}$, and the final group received a higher dose of epidural mixture (0.25% bupivacaine 10 mL with no opioid) followed by intermittent 10 mL boluses of 0.25% bupivacaine as per maternal request. In this meta-analysis, we attempted to minimize the heterogeneity of studies by excluding those which utilized HCs of local anesthetic for test dose or initiation or maintenance of analgesia in the intention-to-treat analysis of data.

Differences in obstetric and anesthetic management may impact the rate of AVD.[4] There was considerable variability in the rates of AVD in the studies included in this meta-analysis, showing that local obstetric practice most likely influences AVD to a greater extent than the anesthetic technique alone. Nevertheless, despite these variations in "baseline" rates of AVD between the different centres performing the studies, the overall rate of AVD is reduced with LCs of local anesthetics. The magnitude of the change in the rate of AVD appears to be consistent as shown by the minimal statistical heterogeneity among the studies ($I^2 = 0$ %). The similar rates of Cesarean delivery between the LC and HC groups suggest that the increased rate of AVD associated with regional anesthesia does not appear to be associated with an increase in Cesarean delivery. This finding is consistent with evidence that epidurals do not increase the rate of Cesarean delivery.[1,33] Prolongation of labour has been

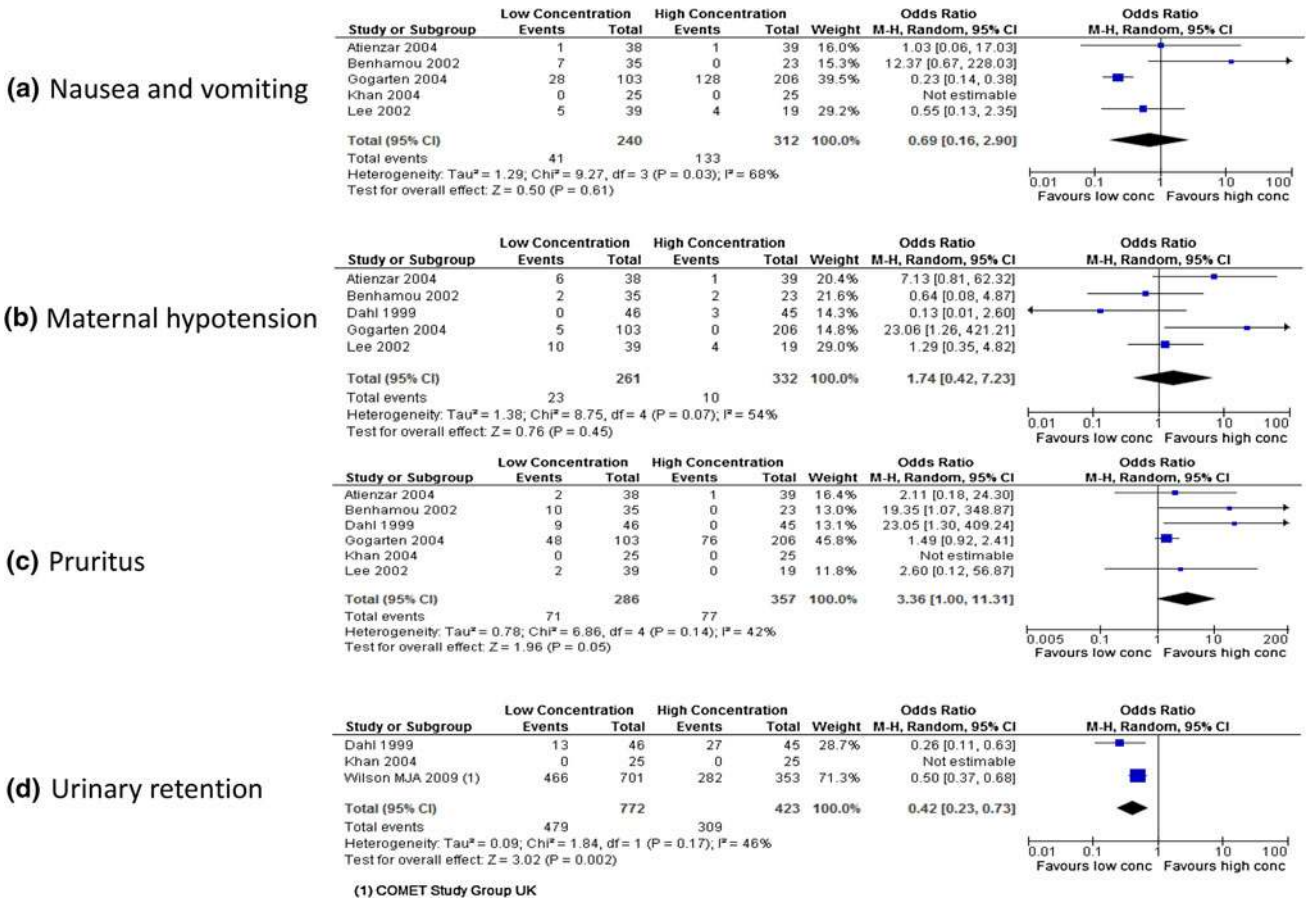

Fig. 6 Forest plots for maternal side effects of A) nausea and vomiting, B) maternal hypotension, C) pruritus, and D) urinary retention

associated with epidural labour analgesia.[1,34,35] The prolonged second stage of labour we observed suggests that this phenomenon may be an effect of the concentration of local anesthetic.

The aim of this study was to show that HCs of local anesthetic are associated with increased AVD. The meta-analysis was designed to show the impact of concentrations of local anesthetic on AVD and not to determine a specific cut-off concentration of local anesthetic beyond which AVD increases. Future dose-finding studies are needed to determine the optimal concentration of local anesthetic to minimize AVD. Additionally, AVD was the primary outcome of interest in designing this study, and the other clinical end points in this meta-analysis should be considered secondary outcome measures.

There were no clinically significant differences in pain scores between the LC and HC groups. For pain scores, we chose a three-hour time point after commencing epidural analgesia. In our view, this interval would most likely reflect the time when analgesia would be achieved by a method to maintain local anesthetic rather than by residual effects of the initial method or agents used to establish the neuraxial blockade. Despite a lower total dose of local anesthetic utilized in the LCs group, there was no subsequent increase in the number of interventions required by the anesthesia care provider to treat labour pain in this group, and maternal satisfaction scores were similar between both groups. Opioid-related side effects, such as pruritus, nausea and vomiting, hypotension, and urinary retention, are well recognized after neuraxial labour analgesia.[15] With the exceptions of a higher incidence of urinary retention in the HCs group ($P = 0.002$), we did not find significant differences in any of these side effects. The trend towards a decreased incidence in pruritus shown in the HCs group may be attributable to the absence of opioid in the HCs groups in two of the six studies.[22,23] Since the opioid utilized varied among the studies (fentanyl,[5,24–27,29,30] sufentanil),[22,23,28,31] the incidence of pruritus caused by the epidural opioid, the opioid dose utilized, and the combination of opioid and type of local anesthetic utilized remain unclear from this meta-analysis.

We hypothesize that the odds of one-minute Apgar scores > 7 favouring the HCs group in this meta-analysis may be due to the higher opioid doses utilized in the LCs

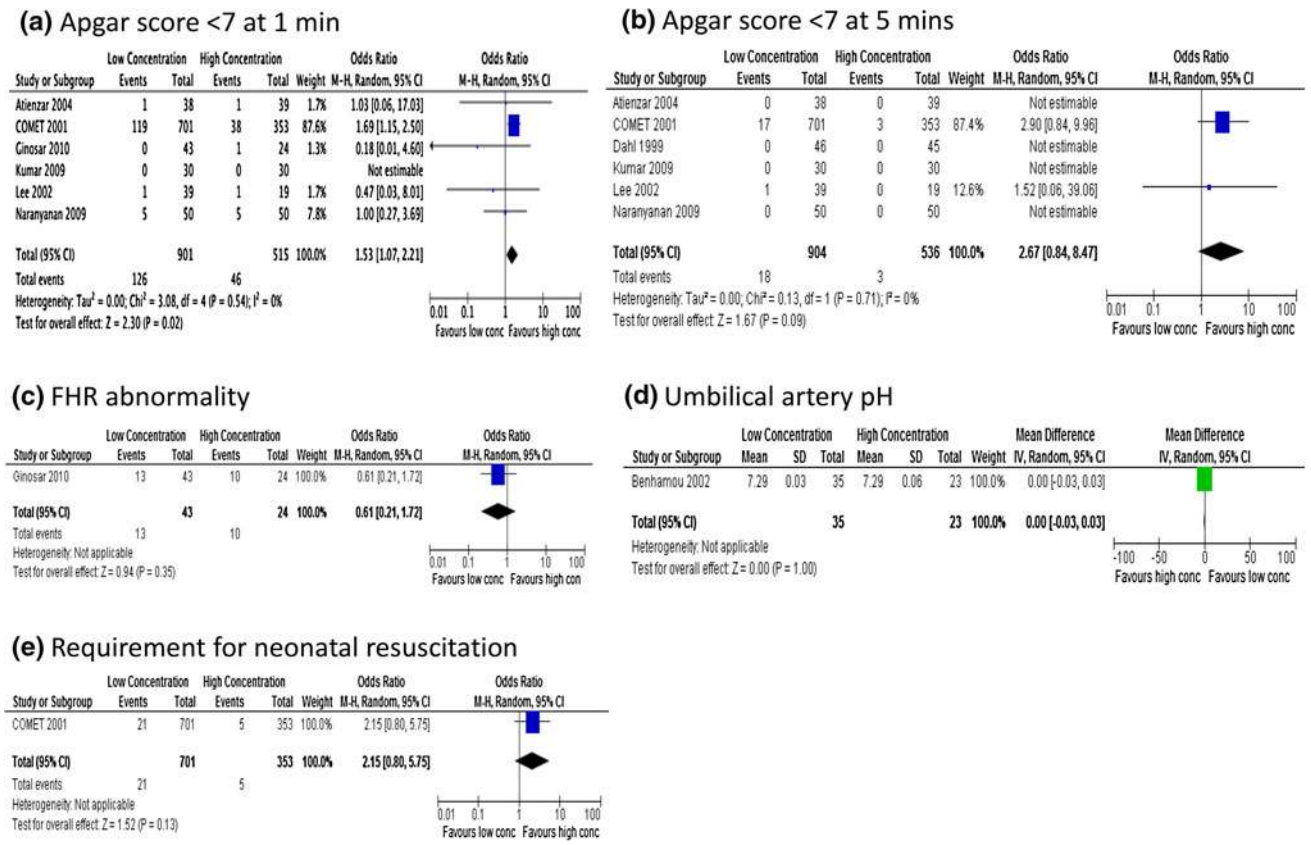

Fig. 7 Forest plots for neonatal outcomes of A) Odds of Apgar score < 7 at one minute and B) at five minutes, C) fetal heart rate (FHR) abnormality, D) umbilical artery pH, and E) requirement for neonatal resuscitation

group. The opioids associated with LCs of local anesthetic solutions may have crossed the placenta and increased early respiratory depression and neonatal sedation in this group. Even so, the Apgar scores must be interpreted with caution since no studies had neonatal outcomes as their primary outcome measure. Most studies did not measure or report fetal outcomes, and all studies were underpowered to find differences between groups. Unlike five-minute Apgar scores, low one-minute scores are not associated with poor developmental outcome.[36] The conclusion from the COMET trial that "possible adverse effects to the neonate should be weighed against the advantages gained by avoidance of an instrumental delivery" with LCs of epidural solutions should still be appreciated.

There are a number of potential limitations of this meta-analysis. While the majority of studies identified favoured LCs, it should be appreciated that the COMET study contributed 63% of the weight of the meta-analysis and therefore makes a substantial contribution to the overall OR. Nevertheless, there was consistency among the included studies when reporting our primary outcome of AVD and other obstetric outcomes (Cesarean delivery, duration of labour). Despite the studies utilizing different techniques and protocols for initiation and maintenance of labour analgesia and various opioid regimens, this meta-analysis shows minimal heterogeneity for the primary outcome. Other limitations include searching only one trial registry (clinicaltrials.gov), variations in methods of grading secondary outcomes, and not all studies reported every outcome. Varying definitions (e.g., pruritus, nausea), measurement intervals and scoring systems (for maternal satisfaction and fetal well-being) made it challenging to determine whether true reproducible differences existed between groups for secondary outcome measurements. We did not control for the timing of epidural placement; however, there appears to be no difference in incidence of AVD between early and late epidural in labour.[37]

In conclusion, LCs ($\leq$ 0.1% bupivacaine or equivalent ropivacaine dose) of labour epidural solutions improve obstetric outcomes (decreased AVD, shorter duration of second stage of labour) and reduce maternal side effects (less motor blockade, better ambulation, and decreased urinary retention) without compromising analgesia. Adverse neonatal effects (lower one-minute Apgar scores) with questionable clinical significance should be weighed against the clear maternal advantages gained. Low concentrations of local anesthetic epidural solutions appear preferable to HCs to optimize obstetric outcome, and on

balance, we would recommend the use of LCs for epidural analgesia for the provision of labour analgesia.

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Conflicts of interest No external funding and no competing interests declared.

Appendix 1: PubMed Search criteria utilized in the study

1. ("ropivacaine"[Supplementary Concept] OR "Bupivacaine"[Mesh] OR bupivacaine[tiab] OR ropivacaine[tiab])
2. ("Obstetric Labor Complications"[Mesh] OR "Labor, Obstetric"[Mesh] OR "Delivery, Obstetric"[Mesh] OR caesarean[ti] OR birth[ti] OR labour[ti] OR labor[ti])
3. (((random*[tiab] OR placebo*[tiab] OR controls[tiab] OR control[tiab] OR controlled[tiab] OR trial[ti] OR "double blind"[tiab] OR blinded[tiab] OR "single blind"[tiab] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) AND (mask*[tiab] OR blind*[tiab])) OR "latin square"[tiab] OR prospectiv*[tiab] OR volunteer*[tiab]) NOT medline[sb]) OR ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR random*[tiab] OR placebo[tiab] OR "clinical trials as topic"[mesh] OR trial[ti])))

Appendix 2: Review Protocol

High *vs* Low concentration of local anesthetic for labour

1st Author_ _ _ _ _ _ _ Year of Publication_ _ _ _ _ _ _

Extracted by_ _ _ _ _ _ _

Methodology

Item	Low Concentration	High Concentration
Number of patients (N)		
Blinded allocation Y/N		
Allocation Concealment		
Random Sequence Generation		
Blinding of participants/ personnel		
Blinding of outcome assessors		
Incomplete data outcome		
Test dose		

Item	Low Concentration	High Concentration
Additive		
Initial dose		
Maintenance		
Population (nullip/mixed)		
SVD n/N		
Assisted vaginal n/N		
Cesarean n/N		
Apgar < 7 n/N one minute		
Apgar < 7 n/N five minutes		
Umbilical pH < 7.2 n/N		
Umbilical pH Mean (SD)		
Need for neonatal rescus n/N		
Duration of 1st stage min (SD)		
Duration of 2nd stage min (SD)		
Clinician top-ups n/N or additional meds requested		
Total dose of local anesthetic mean (SD)		
Pain score		
Bromage = 0 n/N		
Ambulation n/N		
Maternal hypotension n/N		
FHR abnormalities n/N		
Itch n/N (mod/severe)		
Urinary retention		
Maternal satisfaction 1st stage n/N		
Maternal satisfaction 2nd stage n/N		
Nausea /vomiting n/N		
Estimated median duration of analgesia (min)		

Comments:

Appendix 3: Excluded Studies

Bupivacaine Studies:

1. Dennison 1990([63]) –letter.
2. Dresner 1999([64]) -epidural *vs* spinal study.
3. Elliot 1991([65]) -0.125% *vs* 0.25% bupivacaine.
4. Lyons 2007([66]) -0.125% *vs* 0.25% bupivacaine.
5. Marcoux 1987([67]) -0.375% *vs* 0.5% bupivacaine.
6. Olofsson 1997([50]) -0.125% *vs* 0.25% bupivacaine.
7. Olofsson 1998([38]) -0.125% *vs* 0.25% bupivacaine.
8. Stainthorpe 1978([51]) -0.125% *vs* 0.375% *vs* 0.25% bupivacaine.
9. Tan 1994([52]) -0.25% *vs* 0.125% bupivacaine.
10. Thorburn 1981([53]) -0.25% *vs* 0.5% bupivacaine.

11. Handley 1992([54]) -0.125% *vs* 0.1875% *vs* 0.25% bupivacaine.
12. Moir 1975([55]) -0.5% bupivacaine with epinephrine *vs* 0.5% bupivacaine *vs* 2% lidocaine *vs* 2% lidocaine with epinephrine.
13. Harms 1999([56]) -0.0625% *vs* 0.125% *vs* 0.25% bupivacaine. Comparison of initial concentration used to establish block. No infusion was administered.
14. Paech 1993([57]) -0.0625% *vs* 0.125% *vs* 0.25% bupivacaine. Low-dose contained epinephrine.
15. Russell 1995([58]) -0.0625% *vs* 0.125% bupivacaine. Excluded since same cohort of patients used as 1996 study.(45)
16. Scrutton 1998([59]) -Initial concentration used to establish block varied (bupivacaine 0.0625% *vs* 0.125% *vs* 0.25%); however, infusions following initial dose were the same (0.0625% bupivacaine).
17. Cohen 2000([60]) -Initial dose with bupivacaine 0.0625% *vs* 0.125% bupivacaine (with sufentanil). Same infusion concentration and dose in both groups.
18. Christiaens 1998([61]) -0.5% *vs* 0.2% *vs* 0.1% bupivacaine. No infusion, therefore excluded. Study looked at effects of initial bolus concentration only.
19. Brockway 1990([74]) -0.08% *vs* 0.0625% bupivacaine for continuous epidural analgesia in labour. Both concentrations $< 0.1\%$ bupivacaine.
20. Nageotte 1997([75]) -One group received bolus and the other group received infusion. Combined spinal-epidural (CSE) *vs* continuous infusion. Study did not look at the effects of different concentrations. They divided groups by epidural *vs* CSE and whether or not they were encouraged to ambulate.
21. Wang 2010([68]) -Comparison between bupivacaine, ropivacaine, and levo-bupivacaine. No data recorded comparing different concentrations within groups.
22. Sanchez-Pereles 1999([62]) -0.0625% bupivacaine and 1:600,000 epinephrine *vs* 0.125% bupivacaine and 1:800,000 epinephrine. Excluded due to epinephrine.
23. Castro 2000([69]) -Comparison between group 1 (0.0625% bupivacaine with 1:800,000 epinephrine with 20 μg fentanyl at 10 $mL \cdot hr^{-1}$) and group 2 (0.125% bupivacaine with 1:400,000 epinephrine with 20 μg fentanyl at 10 $mL \cdot hr^{-1}$). Excluded due to epinephrine.
24. Shrestha 2007([32]) -Article could not be accessed.
25. Chestnut 1988([49]) - Epinephrine utilized in test dose, test dose utilized 0.5% bupivacaine in the low concentration group, and initial dose utilized was also $> 0.1\%$ in the low concentration group.
26. Lowson 1995([48]) - Test dose and initial dose in low concentration group $> 0.1\%$ bupivacaine.
27. Beilin 2002([47]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
28. Noble 1991([46]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
29. Russell 1996([45]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
30. Ewen 1986([44]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
31. Ferrante 1995([43]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
32. Stoddart 1994([42]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
33. Rodriguez 1990([41]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
34. Li 1985([40]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.
35. Hicks 1988([39]) - Initial dose $> 0.1\%$ bupivacaine in the low concentration group.

Ropivacaine articles:

1) Bernard 2003([70]) -Ropivacaine 0.1 *vs* 0.2%. Varied dose and volume between groups and in early and late labour, and no background infusion.
2) Sia 1999([71]) - Initial dose $> 0.17\%$ ropivacaine in the low concentration group.
3) Boselli 2003([72]) -Ropivacaine 0.1 *vs* 0.15%. Excluded based on concentrations.
4) Beilin 1999([73]) -Ropivacaine 0.2%, 0.15%, 0.1%. Patients given one extra intermittent bolus as required, no background infusion administered. Dose finding study.

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