




A Systematic Review and Meta-Analysis of Randomized Controlled Trials of Labor Epidural Analgesia Using Moderately High Concentrations of Plain Local Anesthetics versus Low Concentrations of Local Anesthetics with Opioids

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Purpose: Compared to low concentrations of local anesthetics with opioids for labor epidural analgesia, very high concentrations of local anesthetics are associated with an increased risk of assisted vaginal delivery. We aimed to investigate if moderately high concentrations of plain local anesthetics are also associated with this risk.

Methods: We searched for published randomized controlled trials that compared moderately high concentrations of plain local anesthetics ($>0.1\%$ but $\leq 0.125\%$ bupivacaine, $>0.1\%$ but $\leq 0.125\%$ levobupivacaine, or $>0.17\%$ but $\leq 0.2\%$ ropivacaine) to low concentrations of local anesthetics ($\leq 0.1\%$ bupivacaine, $\leq 0.1\%$ levobupivacaine, or $\leq 0.17\%$ ropivacaine) with opioids for labor analgesia. Meta-analyses were performed to compare the risk of assisted vaginal delivery and other perinatal outcomes between these two groups.

Results: We identified nine randomized controlled trials with a total of 1334 participants. Meta-analysis of these nine trials showed no differences in the risks of assisted vaginal delivery (odds ratio [OR] = 1.18; 95% confidence interval [CI], 0.93–1.49) or Cesarean delivery (OR = 0.96; 95% CI, 0.71–1.29) between the two groups. The incidence of motor block was higher in the group of moderately high concentrations (OR = 4.05; 95% CI, 2.19–7.48), while the incidence of pruritus was lower (OR = 0.07; 95% CI, 0.03–0.16).

Conclusion: This systematic review and meta-analysis suggests that the current evidence is inadequate to support that moderately high concentrations of plain local anesthetics increase the risk of assisted vaginal delivery compared to low concentrations of local anesthetics with opioids.

Keywords: assisted vaginal delivery, epidural, labor analgesia, local anesthetics, meta-analysis

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Introduction

Neuraxial techniques are the most effective methods for providing intrapartum pain relief. A combination of low concentrations of local anesthetics with opioids is currently the standard for labor epidural analgesia.¹ Compared with high concentrations of local anesthetics, low concentrations of local anesthetics combined with opioids are believed to reduce the incidence of assisted vaginal delivery while providing adequate labor analgesia.

Current definition of low concentrations of local anesthetics for labor epidural analgesia is $\leq 0.1\%$ bupivacaine, $\leq 0.1\%$ levobupivacaine, or $\leq 0.17\%$ ropivacaine.^{2,3} The most recent meta-analysis compared low concentrations versus high concentrations of local anesthetics ($> 0.1\%$ bupivacaine or $> 0.17\%$ ropivacaine) for labor analgesia and concluded that high concentrations of local anesthetics increase the incidence of assisted vaginal delivery.² The conclusion from this meta-analysis was based on the comparison of low concentrations of local anesthetics with multiple different high concentrations of local anesthetics. Previous studies suggested that at a very high concentration, ie, $> 0.125\%$ bupivacaine, $> 0.125\%$ levobupivacaine, or $> 0.2\%$ ropivacaine, epidural local anesthetics with or without opioids were associated with an increased risk of assisted vaginal delivery.^{4,5} However, it is uncertain if current evidence also supports that at moderately high concentrations, ie, $> 0.1\%$ but $\leq 0.125\%$ bupivacaine, $> 0.1\%$ but $\leq 0.125\%$ levobupivacaine, or $> 0.17\%$ but $\leq 0.2\%$ ropivacaine, plain local anesthetics are also associated with such risk. Some studies suggested that plain local anesthetics at a moderately high concentration did not increase the risk of assisted vaginal delivery and provided adequate labor epidural analgesia similar to the standard mixture of low concentration local anesthetics with opioids.^{6,7} We carried out a systematic review and meta-analysis to investigate the existing evidence on this question.

Methods

Definitions of Low, Moderately High, and Very High Concentrations of Local Anesthetics

Low concentrations of local anesthetics were defined as $\leq 0.1\%$ bupivacaine, $\leq 0.1\%$ levobupivacaine, or $\leq 0.17\%$ ropivacaine.^{2,3} The moderately high concentrations of local anesthetics were defined as $> 0.1\%$ but $\leq 0.125\%$ bupivacaine, $> 0.1\%$ but $\leq 0.125\%$ levobupivacaine, or $> 0.17\%$ but $\leq 0.2\%$ ropivacaine, ie, within 25% above the upper limit of low concentrations of local anesthetics. The very high concentrations of local anesthetics were defined as $> 0.125\%$ bupivacaine, $> 0.125\%$ levobupivacaine, or $> 0.2\%$ ropivacaine.

Literature Search Strategies and Data Extraction

This systematic review and meta-analysis were conducted based on criteria of the Preferred Reporting Items for

Systemic Reviews and Meta-analysis (PRISMA) statement. The registration number with PROSPERO is CRD42019145888. We systematically searched Ovid Medline, Cochrane CENTRAL, PubMed, CINAHL and Google Scholars for randomized controlled trials (RCTs) that compared moderately high concentrations of plain local anesthetics versus low concentrations of local anesthetics with opioids for maintenance of labor epidural analgesia.

Search terms included epidural analgesia, epidural anesthesia, labor, delivery, obstetrics, bupivacaine, levobupivacaine, ropivacaine, randomized, trial (see [Appendix 1](#) for database search strategy for Ovid Medline). We also manually searched for studies listed in the references of included papers, in case there were potential studies not captured by the database search strategy. There was no limitation on language.

We included original full-text articles that were: (1) RCTs published in peer-reviewed journals from 1946 (the earliest year that publications are searchable in the online databases) to April 2020, (2) compared epidural infusion of moderately high concentrations of plain local anesthetics versus low concentrations of local anesthetics with opioids, (3) assessed outcomes including spontaneous delivery, assisted vaginal delivery (vaginal delivery with the help of forceps or a vacuum device), cesarean delivery, duration of labor, analgesia effect, motor block, nausea, vomiting, maternal hypotension, pruritus, urinary retention, neonatal Apgar scores, and umbilical blood pH. If there were several studies based on the same cohort, the studies with the most recent and relevant results were included.

Study selection was conducted in three screening steps. The first screening of titles was independently reviewed by two reviewers (LZ, XZ) by reviewing the titles identified from the literature search. The second screening of study abstracts that remained from the initial title screening were then reviewed by three reviewers, among whom disagreements were reconciled (LZ, XZ and XW). In the third screening, full-text studies that met the above inclusion criteria were included for final systematic review and meta-analyses. Data were collected and verified from included studies by two reviewers (LZ, XZ) independently.

Characteristics of each study, including study design, patient baseline information, procedural details and above-mentioned outcomes, were extracted into Microsoft-Excel file. [Figure 1](#) summarized the complete process of paper study enrollment according to the PRISMA statement.

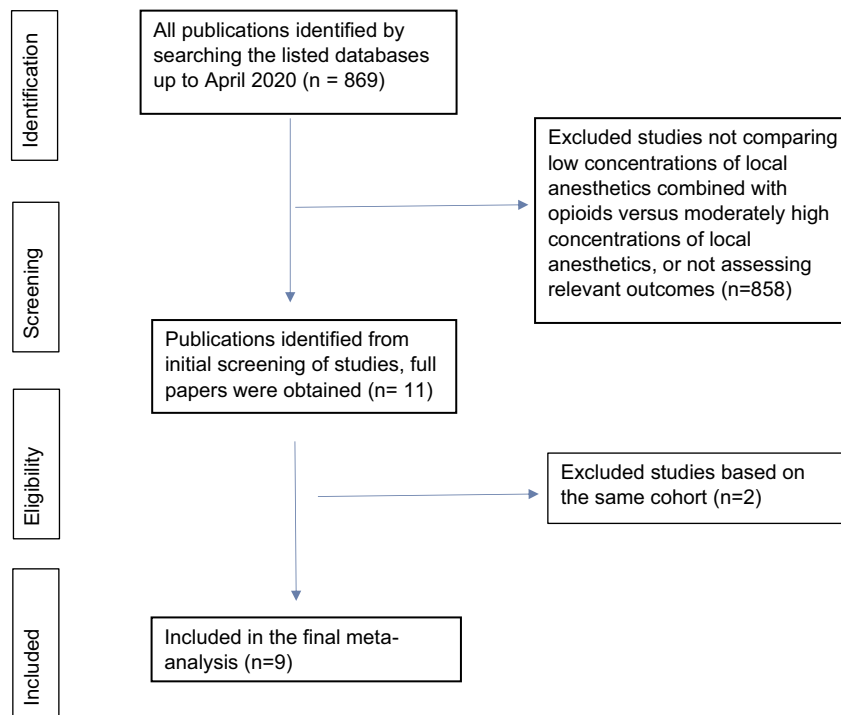


Figure 1 Flow chart for literature enrollment from identification to final synthesis according to the PRISMA protocol.
Abbreviation: PRISMA, Preferred Reporting Items for Systemic Reviews and Meta-analysis.

Quality Assessment

The included studies were independently evaluated by two reviewers (LZ, XZ) using the Cochrane risk of bias assessment tool,^{8,9} which evaluated 6 domains including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

Statistical Analyses

The primary outcome was the incidence of assisted vaginal delivery. Secondary outcomes included (1) obstetric outcomes (incidence of cesarean delivery, incidence of spontaneous vaginal delivery, duration of first stage of labor, duration of second stage of labor); (2) analgesic effect (pain scores); (3) maternal side effects (motor block (no motor block is defined as a Bromage grade = I), pruritus, nausea, vomiting, maternal hypotension, and urinary retention); (4) neonatal outcomes (neonatal Apgar scores < 7 at one and five minutes, and umbilical arterial blood pH).

Random-effects meta-analyses were performed for each included outcome. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for binary outcomes, while mean differences (MDs) and 95% CIs were estimated for continuous outcomes. The pooled OR is considered statistically significant if the 95% CI did not contain 1, and the

pooled MD is considered statistically significant if the 95% CI did not contain 0. Each included study's pooled estimates and measures of variability were used to generate forest plots. If meta-analysis was not possible for an outcome, the data from individual studies were reported qualitatively. Heterogeneity was assessed using the I^2 statistic. The I^2 statistic was calculated to quantify the proportion of between-study heterogeneity attributable to variability in the association rather than sampling variation. The p value was calculated based on the heterogeneity test (I^2), where a high p value (≥ 0.05) indicated that the heterogeneity was insignificant. All analyses were conducted using RStudio (Version 1.0.136; The R Foundation, Vienna, Austria) using the "Meta" and "Metafor" package.

Results

Study Characteristics and Risk of Bias Assessment

The database started with a total of 869 citations. Of these, 858 studies were excluded due to irrelevant topics, assessment of exposure and outcomes not meeting the inclusion criteria. The remaining 11 studies were retrieved in full-text to be examined in more details. Three studies^{7,10,11} were based on the same cohort and the study with the most

recent and relevant results was included,⁷ resulting in a total of 9 studies included in the systematic review and meta-analysis (Figure 1). Table 1 presents study characteristics of included studies. There are 9 RCTs and a total of 1334 patients included.^{6,7,12–18} Basal infusion was used for labor epidural analgesia in all but one RCT.¹⁸ Sample size ranged from 32 to 587, with median being 80. The risk of bias assessment is shown in Appendix 2.

Meta-Analyses

Mode of Delivery

Nine studies with 1334 participants compared the mode of delivery between the group of moderately high concentrations of plain local anesthetics and the group of low concentrations of local anesthetics with opioids. There were no significant differences in the odds of assisted vaginal delivery (OR = 1.18; 95% CI, 0.93–1.49; $I^2 = 0\%$, $p = 0.67$), Cesarean delivery (OR = 0.96; 95% CI, 0.71–1.29; $I^2 = 0\%$, $p = 0.78$), or spontaneous vaginal delivery (OR = 0.89; 95% CI, 0.71–1.11; $I^2 = 0\%$, $p = 0.89$) (Figure 2).

Duration of Labor

Four studies with 926 participants reported outcomes for the duration of the first stage of labor, and four studies with 389 participants presented outcomes for the duration of the second stage of labor. Meta-analysis indicated that the duration of the first stage of labor was shorter in the group of moderately high concentrations of plain local anesthetics (MD = -32.84 minutes; 95% CI, -63.81 – -1.87 minutes; $I^2 = 0\%$, $p = 0.54$), while the duration of the second stage of labor was not significantly different between two groups (MD = 0.87 minutes; 95% CI, -5.02–6.76 minutes; $I^2 = 6\%$, $p = 0.36$) (Figure 3).

Analgesic Effect

Eight studies with 747 participants compared pain scores between the two groups (Table 2). A variety of methods were used to report pain scores in those studies, which made it unfeasible to perform a meta-analysis. Among these eight studies, six studies with 613 participants reported no significant difference in pain scores between the two groups. One study with 50 participants¹⁷ reported a slightly lower pain score at 30 minutes in the group of moderately high concentration of local anesthetics, while another study¹⁴ with 84 participants reported a slightly higher pain score at 15 minutes, 30 minutes, 60 minutes, and 90 minutes in the group of moderately high concentration of local anesthetics. Nevertheless, in both studies, pain scores were not

significantly different between the two groups at other times of assessment. Three studies with 315 participants reported pain relief assessed either by patients^{6,12} or midwives.¹⁵ No significant difference in pain relief was found between the two groups.

Maternal Side Effects

Nine studies with 1215 participants presented results for motor block. The group of moderate high concentrations of local anesthetics was associated with higher odds of motor block (OR = 4.05; 95% CI, 2.19–7.48; $I^2 = 60\%$, $p = 0.01$) (Figure 4A). Six studies with 460 participants reported results for pruritus. The group of moderate high concentrations of local anesthetics was associated with lower odds of pruritus (OR = 0.07; 95% CI, 0.03–0.16; $I^2 = 2\%$, $p = 0.38$) (Figure 4B). The odds of nausea (OR = 0.98; 95% CI, 0.59–1.60; $I^2 = 0\%$, $p = 0.62$), vomiting (OR = 1.01; 95% CI, 0.57–1.80; $I^2 = 0\%$, $p = 0.91$), maternal hypotension (OR = 0.74; 95% CI, 0.15–3.70; $I^2 = 59\%$, $p = 0.06$), and urinary retention (OR = 0.94; 95% CI, 0.30–2.90; $I^2 = 51\%$, $p = 0.13$) were not significantly different between the two groups (Figure 4C–F).

Neonatal Outcomes

Five studies with 788 participants compared neonatal Apgar scores at one minute and five minutes between the group of moderately high concentrations of plain local anesthetics and the group of low concentrations of local anesthetics with opioids. There were no significant differences in the odds of neonatal Apgar scores < 7 at one minute (OR = 0.93; 95% CI, 0.61–1.41; $I^2 = 0\%$, $p = 0.88$), or five minutes (OR = 2.50; 95% CI, 0.33–18.70; $I^2 = 20\%$, $p = 0.29$) (Figure 5A and B). Three studies with 751 participants compared umbilical arterial blood pH between the two groups. There were no significant differences (MD = -0.01; 95% CI, -0.02–0.01; $I^2 = 45\%$, $p = 0.16$) (Figure 5C).

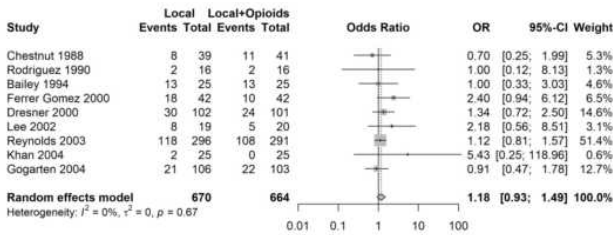
Discussion

The combination of low concentrations of local anesthetics with opioids has been commonly used for labor epidural analgesia.¹ This combination is widely accepted as the standard mixture partially due to its suggested benefits to decrease the risk of assisted vaginal delivery while providing adequate labor analgesia.^{2,4} Although previous studies suggested that at a very high concentration, epidural local anesthetics with or without opioids increased the risk of assisted vaginal delivery,^{4,5} our systemic review and meta-analysis demonstrated that current evidence is inadequate

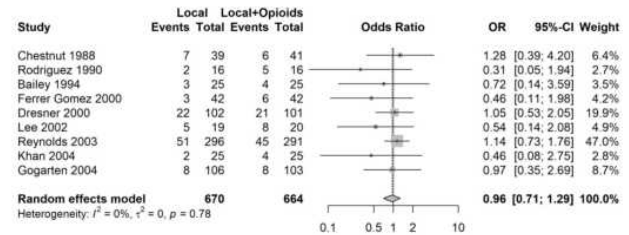
Table 1 Baseline Characteristics of Included Clinical Trials

Studies	Region	Population	Sample Size		Drugs		Dose		Mode of Maintenance
			Local	Local + Opioids	Local	Local + Opioids	Local	Local + Opioids	
Chestnut 1988	USA	Nulliparous	39	41	0.125% bupivacaine	0.0625% bupivacaine + 2 µg/mL of fentanyl	12.5 mL/hour	12.5 mL/hour	Continuous infusion with clinician bolus
Rodriguez 1990	USA	Mixed	16	16	0.125% bupivacaine	0.0625% bupivacaine + 20 µg/mL of butorphanol	12 mL/hour	12 mL/hour	Continuous infusion with clinician bolus
Bailey 1994	UK	Mixed	25	25	0.125% bupivacaine	0.0625% bupivacaine + 5 µg/mL of diamorphine	10 mL/hour	10 mL/hour	Continuous infusion with clinician bolus
Ferrer Gomez 2000	Spain	Mixed	42	42	0.2% ropivacaine	0.1% ropivacaine + 2 µg/mL of fentanyl	6 to 10 mL/hour	6 to 10 mL/hour	Continuous infusion with clinician bolus
Dresner 2000	UK	Mixed	102	101	0.2% ropivacaine	0.1% bupivacaine + 2 µg/mL of fentanyl	8 mL/hour	8 mL/hour	Continuous infusion with clinician bolus
Lee 2002	China	Nulliparous	19	20	0.2% ropivacaine	0.1% ropivacaine + 2 µg/mL of fentanyl	10 mL/hour	10 mL/hour	Continuous infusion with clinician bolus
Reynolds 2003	UK	Mixed	296	291	0.125% bupivacaine	0.0625% bupivacaine + 2.5 µg/mL of fentanyl or 0.25 µg/mL of sufentanil	12 mL/hour	12 mL/hour	Continuous infusion with clinician bolus
Khan 2004	India	Mixed	25	25	0.125% bupivacaine	0.0625% bupivacaine + 1 µg/mL of fentanyl	8 mL/hour	8 mL/hour	Continuous infusion
Gogarten 2004	Belgium and Germany	Mixed	106	103	0.2% ropivacaine	0.125% ropivacaine + 0.75 µg/mL of sufentanil	4 mL bolus with a lockout interval of 15 minutes	4 mL bolus with a lockout interval of 15 minutes	Patient controlled epidural analgesia without background infusion

A Assisted Vaginal Delivery



B Cesarean Delivery



C Spontaneous Vaginal Delivery

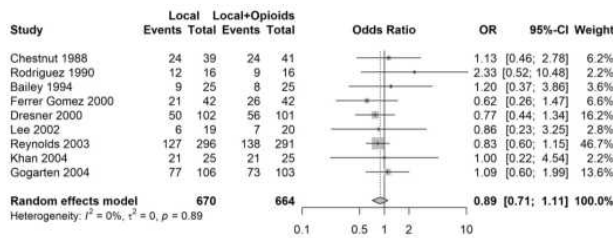
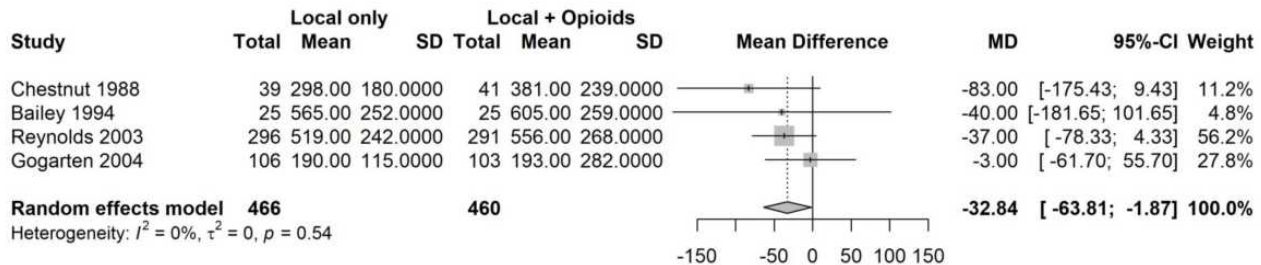


Figure 2 Forest plot of odds of assisted vaginal delivery (A), Cesarean delivery (B), and spontaneous vaginal delivery (C). There are no significant differences between the group of moderately high concentrations of plain local anesthetics and the group of low concentrations of local anesthetics with opioids.

Abbreviations: OR, odds ratio; CI, confidence interval.

A Duration of Labor (First Stage)



B Duration of Labor (Second Stage)

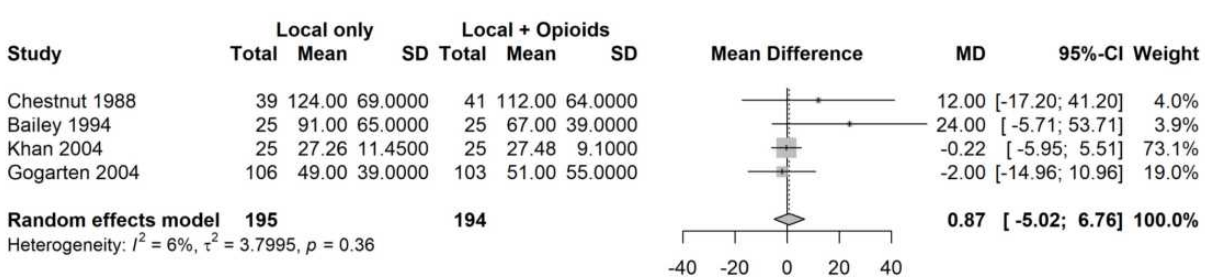


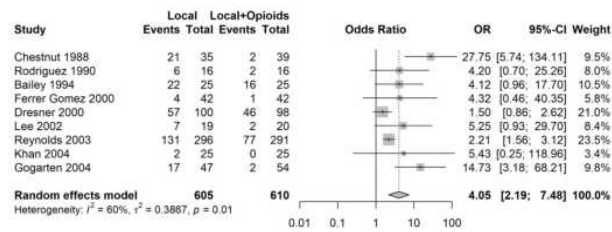
Figure 3 Forest plot of duration of first stage (A) and second stage of labor (B). Moderately high concentrations of local anesthetics are associated with a small but significant decrease in the duration of first stage of labor but no significant change in the duration of second stage of labor.

Abbreviations: MD, mean difference; CI, confidence interval.

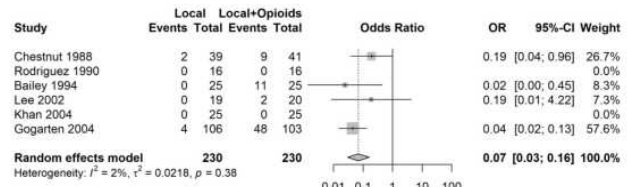
Table 2 Maternal Pain Score and Pain Relief

Studies	Region	Population	Sample Size		Timing of Assessment	Pain Scores		Pain Relief
			Local	Local + Opioids		Local versus Local + Opioids	Local versus Local + Opioids	
Chestnut 1988	USA	Nulliparous	39	41	0, 15, 30 minutes after the test dose, and then every 30 minutes.	No difference	No difference	No difference
Rodriguez 1990	USA	Mixed	16	16	15, 30, 45, 60 minutes after the initial dose, and then every 30 minutes.	No difference	No difference	No difference
Bailey 1994	UK	Mixed	25	25	30 minutes after the test dose, and then every 60 minutes.	No difference	NA	NA
Ferrer Gomez 2000	Spain	Mixed	42	42	0, 5, 10, 15, 30, 60, 90, 120 minutes after the initial dose.	Slightly higher pain scores at 15, 30, 60, 90 minutes in Local group; no difference at other times	NA	NA
Dresner 2000	UK	Mixed	102	101	30 minutes after the initial dose. Scores for first and second stage obtained 24 hours after delivery.	No difference	No difference	No difference
Lee 2002	China	Nulliparous	19	20	0, 10, 20, 30, 60 minutes after the initial dose, and then every 60 minutes.	No difference	NA	NA
Khan 2004	India	Mixed	25	25	15, 30, 60, 90 minutes after the initial dose.	Slightly lower pain score at 30 minutes in Local group; no difference at other times	NA	NA
Gogarten 2004	Belgium and Germany	Mixed	106	103	0, 10, 20, 60 minutes after the initial dose, and then every 60 minutes.	No difference	NA	NA

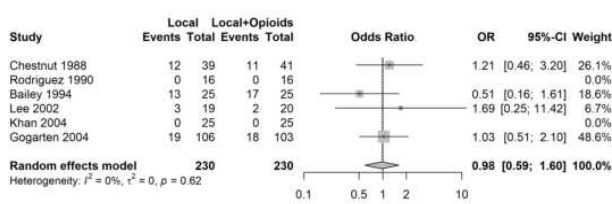
A Motor Block



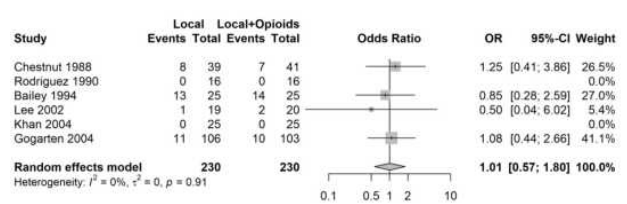
B Pruritis



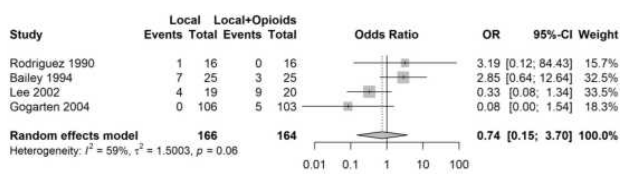
C Nausea



D Vomiting



E Maternal Hypotension



F Urinary Retention

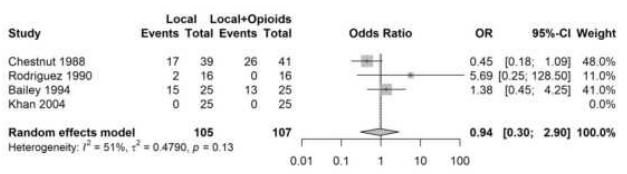


Figure 4 Forest plot of maternal side effects including motor block (A), pruritus (B), nausea (C), vomiting (D), maternal hypotension (E) and urinary retention (F). Moderately high concentrations of local anesthetics are associated with increased odds of motor block but decreased odds of pruritus. There are no significant differences in nausea, vomiting, maternal hypotension or urinary retention between the two groups. **Abbreviations:** OR, odds ratio; CI, confidence interval.

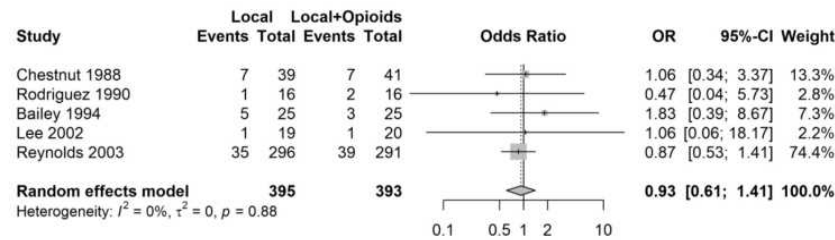
to support the assumption that at moderately high concentrations, plain local anesthetics also increase such risk. Findings from this meta-analysis suggested that, compared to low concentrations of local anesthetics with opioids, moderately high concentrations of plain local anesthetics provided effective labor analgesia without increasing the risk of assisted vaginal delivery. This might not be surprising as none of included trials showed a significant difference in mode of delivery between the two groups.

Our findings are different from those of a previous meta-analysis comparing low concentrations of local anesthetics to high concentrations of local anesthetics for labor analgesia.² In that meta-analysis, low concentrations of local anesthetics were associated with a decreased risk of assisted vaginal delivery. The definition of low concentrations of local anesthetics in that meta-analysis was the same as ours, ie, $\leq 0.1\%$ bupivacaine or $\leq 0.17\%$ ropivacaine. However, in that meta-analysis, they included both moderately high concentrations of local anesthetics and very high concentrations of local anesthetics in a single group. In this meta-analysis, we separated them and focused only on moderately high concentrations. It is likely that very high concentrations of local anesthetics

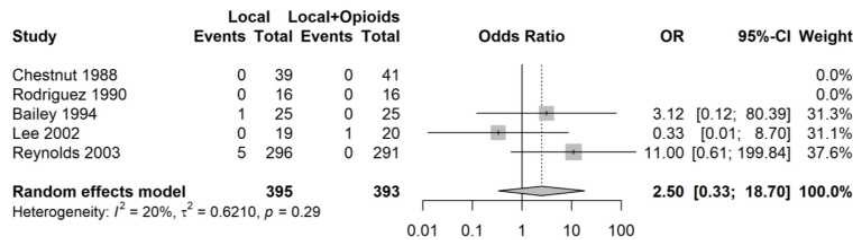
increase the risk of assisted vaginal delivery, but moderately high concentrations might not.

Our meta-analysis has several limitations. First, due to the limited number of available RCTs, we had to pool all low concentrations of local anesthetics into one group, and did not divide different low concentrations or different local anesthetics into different groups. However, this limitation might not affect our analysis significantly. Moderately high concentrations of plain local anesthetics were compared to very low concentrations of local anesthetics in the majority of the included trials – 0.0625% bupivacaine was used in five trials and 0.1% ropivacaine was used in the other two trials. The increased risk of assisted vaginal delivery was not detected in any of these seven trials. Second, all but one clinical trial included in this meta-analysis used the method of continuous infusion instead of intermittent bolus for epidural analgesia. It is unclear if moderately high concentrations of local anesthetics, when given as intermittent bolus, would increase the risk of assisted vaginal delivery. The only available trial included in this meta-analysis suggested that they did not. However, more trials are needed to clarify this question. Third, we did not compare moderately high

A Apgar Scores at One Minute



B Apgar Scores at Five Minutes



C Neonatal Umbilical Arterial Blood pH

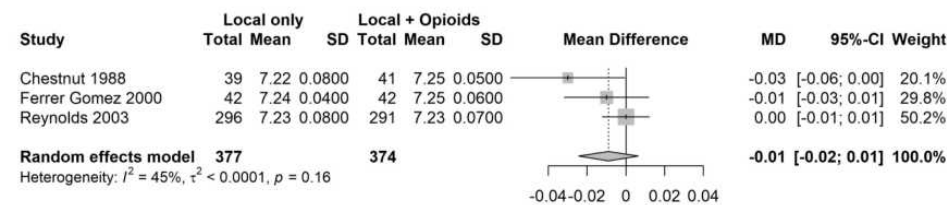


Figure 5 Forest plot of neonatal Apgar scores at one minute (A) and five minutes (B), and neonatal umbilical arterial blood pH (C). There are no significant differences in Apgar scores or umbilical arterial blood pH between the two groups.

Abbreviations: OR, odds ratio; MD, mean difference; CI, confidence interval.

concentrations of plain local anesthetics with low concentrations of plain local anesthetics. Although low concentrations of plain local anesthetics might be able to decrease the incidence of assisted vaginal delivery, previous studies suggested that they are unlikely able to provide adequate labor epidural analgesia.^{19,20} Fourth, all the available studies included in this meta-analysis are old with the most recent one being published in 2004. Maintenance regimens in the included studies likely differ from those employed in contemporary practice. None of the studies except one used patient controlled epidural analgesia (PCEA), which is a standard practice in many institutions currently. In addition, we could not pool the results for pain scores because a variety of methods were used to report pain scores in the included studies. We also did not report on need for physician interventions as such information was absent in most of the included studies. Future studies utilizing contemporary regimens for labor epidural analgesia and reporting pain scores with a standard method will help address this limitation.

One disadvantage of the current standard mixture which includes opioids is the iatrogenic exposure of parturients to opioids. Although such exposure may not increase the risk of opioid addiction, it is associated with opioid-induced side effects such as itching. Furthermore, the opioid epidemic has been getting worse, and the prevalence of opioid abuse or dependence during pregnancy also increased significantly in recent years.^{21,22} To deal with the worsening opioid epidemic and prevent opioid diversion, many hospitals are implementing more restricted policies on handling opioid-containing medications and wastes. This results in additional financial burdens, time consumption, and potential documentation errors for using epidural cartridges containing opioids. A variety of adjunct agents have been studied to replace opioids for labor epidural analgesia,^{23–26} however, none of them have been widely accepted by obstetric anesthesiologists or pharmaceutical companies as a replacement for the current standard mixture that contains opioids. This is either due to unclear superiority of those agents over opioids or uncertain profits for producing non-standard epidural

mixtures in a large scale. If future trials with larger sample sizes could demonstrate that moderately high concentrations of plain local anesthetic are safe and effective for labor epidural analgesia, one solution might be to remove opioids and use moderately high concentrations of plain local anesthetics for labor epidural analgesia.

Conclusion

In conclusion, this systematic review and meta-analysis suggested current evidence is inadequate to support the assumption that moderately high concentrations of plain local anesthetics increase the risk of assisted vaginal delivery compared to standard mixture of low concentrations of local anesthetics with opioids.

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Disclosure

Li Zhang, Yirui Hu, Xianren Wu, Michael J. Paglia, Xiaopeng Zhang report no conflicts of interest in this work.

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