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The impact of epidural ropivacaine versus levobupivacaine for labor analgesia on maternal and fetal outcomes: a meta-analysis

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Abstract

Introduction Newer neuraxial local anesthetic agents which have been used as epidural analgesia have shown to provide reliable pain relief during labor. Ropivacaine and levobupivacaine are newer agents now used for labor analgesia. However, even though few studies have made their comparison with bupivacaine, ropivacaine and levobupivacaine have seldom systematically been compared. Therefore, in this analysis, we aimed to systematically show the impact of epidural ropivacaine versus levobupivacaine for labor analgesia on maternal and fetal outcomes.

Methods http://www.clinicaltrials.gov, Web of Science, MEDLINE, EMBASE, Cochrane database and Google Scholar were searched for studies comparing ropivacaine versus levobupivacaine for labor analgesia. Maternal and fetal outcomes were considered as the endpoints in this analysis. The RevMan software 5.4 was used to analyze data in this study. Risk ratio (RR) with 95% confidence intervals (CI) were used to represent the data post analysis.

Results A total number of 2062 participants were included in this analysis whereby 1054 participants were assigned to ropivacaine and 1008 participants were assigned to levobupivacaine. The main results of this analysis showed that epidural ropivacaine was not associated with significantly higher risk of hypotension (RR: 0.71, 95% CI: 0.43 – 1.17; $P=0.18$) and pruritus (RR: 1.12, 95% CI: 0.89 – 1.42; $P=0.34$) when compared to levobupivacaine for labor analgesia. However, the risk of nausea and vomiting was significantly higher with ropivacaine (RR: 1.60, 95% CI: 1.05 – 2.44; $P=0.03$). Spontaneous vaginal delivery (RR: 0.99, 95% CI: 0.89 – 1.42; $P=0.83$), instrumental vaginal delivery (RR: 1.13, 95% CI: 0.89 – 1.45; $P=0.32$) and the risk for cesarean section (RR: 0.76, 95% CI: 0.42 – 1.37; $P=0.35$) were not significantly different. When fetal outcomes were assessed, Apgar score < 7 at 1 min (RR: 1.01: 95% CI: 0.57 – 1.80; $P=0.97$), abnormality of fetal heart rate (RR: 1.45, 95% CI: 0.55 – 3.79; $P=0.45$) and neonatal asphyxia (RR: 0.35, 95% CI: 0.10 – 1.18; $P=0.09$) were also similarly manifested.

Conclusions To conclude, our analysis showed both epidural ropivacaine and levobupivacaine to be equally effective for labor analgesia in terms of maternal and fetal outcomes. No major adverse maternal and fetal outcome was observed in this analysis. However, considering the several limitations of this analysis, further larger studies should be able to solve and clarify this issue.

Keywords Epidural anesthesia, Ropivacaine, Levobupivacaine, Labor analgesia, Spontaneous vaginal delivery, Instrumental delivery, Cesarean section, Hypotension, Pregnancy

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Introduction

Today, in order to facilitate delivery without significant pain, modern obstetric analgesia has been introduced [1]. Its aim has been to reduce pain perception during cervical dilatation and uterine contraction during delivery of the fetus [2].

Newer neuraxial local anesthetic agents which have been used as epidural analgesia have shown to provide reliable pain relief during this labor and delivery process [3]. In the beginning, bupivacaine was used as the local anesthetic agent for pain relief during labor [4]. However, due to common central nervous system toxicity even with minimal dosage (1.25 mg/kilogram) [5], alternative anesthetic agents that could potentially have less toxicity to the central nervous and the cardiovascular systems were searched.

Ropivacaine and levobupivacaine are two newer agents now used for labor analgesia [6]. These two most recently introduced local anesthetic agents might have more benefits in comparison to other anesthetic agents used. Scientific reports have shown ropivacaine and levobupivacaine to have less motor blocking properties at equal milligram dosages when compared to bupivacaine [7]. The low motor blocking property of ropivacaine could be associated with the fact that the drug has a lower lipophilic capacity thus preventing its penetration into the myelinated nerve fibers [8].

Ropivacaine has been the focus of interest due to its higher cardiovascular safety compared to the previously used bupivacaine [9] whereas levobupivacaine could offer a greater margin of clinical safety when compared to bupivacaine [10]. However, even though few studies have made their comparison with bupivacaine, for example, Li et al. who compared the effectiveness of bupivacaine and fentanyl versus ropivacaine and fentanyl in epidural anesthesia for labor pain showed both drugs to be comparable [11]. Similarly, Bhatia et al. [12] again showed bupivacaine and ropivacaine to be equally effective. However, a comparison of ropivacaine versus levobupivacaine for labor analgesia has seldom systematically been carried out. Therefore, in this analysis, we aimed to systematically show the impact of epidural ropivacaine versus levobupivacaine for labor analgesia on maternal and fetal outcomes.

Methods

Search databases

From May 2024 to June 2024, http://www.clinicaltrials.gov, Web of Science, MEDLINE, EMBASE, Cochrane database and Google Scholar were searched for studies comparing ropivacaine versus levobupivacaine for labor analgesia.

Search strategies

The following search terms were considered during this search process:

- Epidural ropivacaine, levobupivacaine and labor analgesia;
- Ropivacaine, levobupivacaine and labor;
- Ropivacaine, levobupivacaine and pregnancy outcomes;
- Ropivacaine versus levobupivacaine and delivery;
- Newer epidural analgesia;
- Newer epidural anesthesia for labor.

Inclusion and exclusion criteria

Studies were included if:

(a) They were randomized trials or observational studies which compared epidural ropivacaine versus levobupivacaine for labor analgesia;
(b) They reported maternal or fetal outcomes;
(c) They were published in English.

Studies were excluded if:

(a) They were literature reviews, brief reviews, systematic reviews and meta-analyses;
(b) They did not report maternal or fetal outcomes;
(c) They were not published in English;
(d) They consisted of data in a form that could not be used in this analysis;
(e) They were repeated studies.

Data extraction and quality assessment

The authors independently extracted data. Data which were extracted included the names of the authors, the publication year, the time period of patients' enrollment, the total number of participants which were assigned to the ropivacaine group and the levobupivacaine group respectively, the maternal and fetal outcomes, the baseline features of the participants, the general features of the studies, the types of studies, the total number of events associated with each outcome, and the methodological quality of the studies.

Quality assessment of the randomized trials was carried out based on the recommendations suggested by the Cochrane collaboration [13] whereas the Newcastle Ottawa scale (NOS) [14] was used to assess the methodological quality in observational studies.

An essential component of systematic reviews is the assessment of the risk of bias. Bias arises due to confounding factors, inappropriate criteria for the

selection of participants, minor errors in the measurement of outcomes, departures from the intended exposure, missing outcome data and selective reporting. The validity of the studies that have been included in the systematic review has been assessed and the extent to which that might underestimate or overestimate the true effects, called the risk of bias, is considered vital in systematic reviews.

For the maintenance of transparency in the systematic review findings, a risk of bias assessment was performed for each included randomized study. The recommendations suggested by the Cochrane collaboration included:

- Random sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding of participants and personnel (performance bias);
- Blinding of outcome assessment (detection bias);
- Incomplete outcome data (attrition bias);
- Selective reporting (reporting bias);
- Other bias.

The NOS was used to assess bias risk for the non-randomized trials. This tool was developed to assess the quality of non-randomized studies based on its design, content and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. A 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies respectively:

(a) Selection:

- Representative of the exposed cohort;
- Selection of the external control;
- Ascertainment of exposure;
- Outcome of interest not present at the start of the study.

(b) Comparability:
- Main factor and additional factor based on comparability of cohorts.

(c) Outcome:

- Assessment of the outcomes;
- Sufficient follow-up time period;
- Adequacy of follow-up.

Statistical analysis

The RevMan software 5.4 was used to analyze data in this study. Risk ratio (RR) with 95% confidence intervals (CI) were used to represent the data post analysis.

Heterogeneity is apparent in meta-analyses. Heterogeneity was assessed by two methods: the Q statistic test whereby a subgroup analysis with a *P* value less or equal to 0.05 was considered statistically significant and a subgroup analysis with a *P* value greater than 0.05 was considered insignificant statistically; and the I^2 statistic test whereby an increasing I^2 value denoted an increasing heterogeneity whereas a low I^2 value denoted a low heterogeneity. If the I^2 value was below 50%, a fixed effect statistical model was used whereas a random effect statistical model was used if an I^2 value above 50% was obtained.

A sensitivity analysis was also carried out by a method of exclusion whereby each study was excluded one by one and a new analysis was conducted each time to see any significant difference in comparison to the main result of this analysis.

Publication bias was also assessed by observing funnel plots.

Compliance with ethical guidelines

No author was involved in any experiment conducted on animals or humans. Therefore, an ethical approval was not required for this meta-analysis.

Results

Search outcomes

The Preferred reporting items in systematic reviews and meta-analyses (PRISMA) guideline was followed [15]. Our search resulted in a total number of 228 publications. After an initial assessment of the titles and abstracts, 175 publications were eliminated. Fifty three (53) full text articles were assessed for eligibility.

Further eliminations were carried out. Two articles did not report maternal or fetal outcomes whereas another 5 articles were literature reviews/brief reviews, and 7 were case studies while 26 were duplicated studies. Finally, only 13 studies [16–28] were selected for this analysis. The flow diagram for study selection has been illustrated in Fig. 1.

General features of the studies

The general features of this study have been given in Table 1. A total number of 2062 participants were included in this analysis whereby 1054 participants were assigned to ropivacaine and 1008 participants were assigned to levobupivacaine as shown in Table 1. Most of

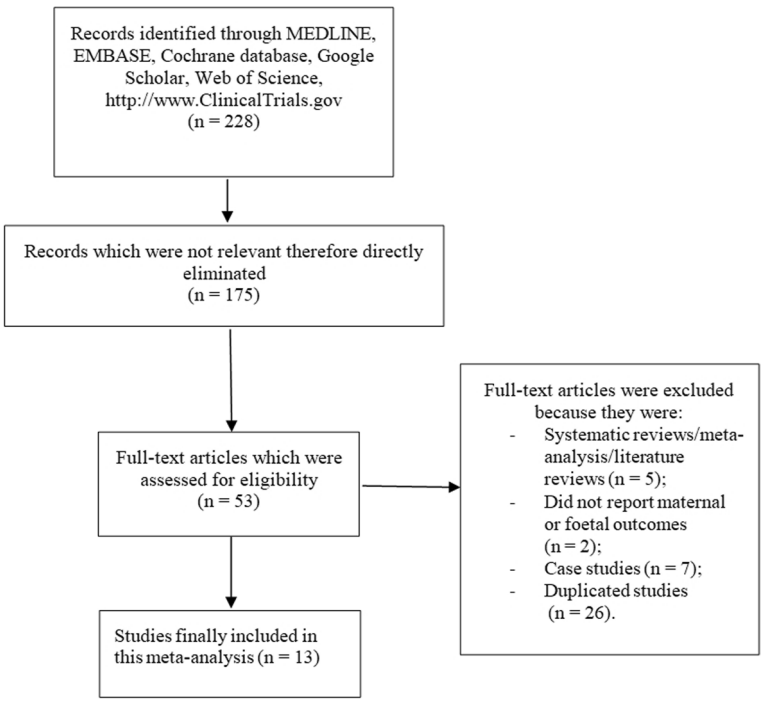

Fig. 1 Flow diagram showing the study selection

Table 1 General features of the included studies

Studies	Type of study	Participants enrollment period (years)	No of participants assigned to Ropivacaine (n)	No of participants assigned to Levobupivacaine (n)
Atienzar 2008 [16]	Randomized trial	-	34	32
Beilin 2007 [17]	Randomized trial	-	90	34
Boulier 2009 [18]	Randomized trial	2006	17	16
Buyse 2007 [19]	Randomized trial	-	24	25
Camorcia 2005 [20]	Randomized trial	-	32	33
Cheng 2019 [21]	Retrospective analysis	2016—2017	318	297
Kim 2013 [22]	Randomized trial	-	30	30
Lee 2011 [23]	Retrospective study	2007	193	199
Purdie 2004 [24]	Randomized trial	-	26	28
Sah 2006 [25]	Prospective randomized trial	-	50	54
Sia 2005 [26]	Randomized trial	-	50	50
Velde 2007 [25]	Randomized trial	-	142	146
Zhao 2019 [26]	Observational	2015—2018	48	64
Total no of patients (n)			1054	1008

the studies were randomized trials. The bias risk assessment of the randomized and non-randomized studies have been illustrated in Table 2.

Baseline features of the participants

The baseline features of the participants have been listed in Table 3. The mean age of the participants varied from 26.0 to 33.4 years and the mean weight ranged from 65.0 to 83.5 kg as shown in Table 3. The mean height of the participants varied from 156 to 167 cm and the mean gestational age varied from 38.5 to 41 weeks as shown in Table 3.

Table 2 The methodological quality assessment of the studies

For the randomized trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Atienzar 2008 [16]	√	√	√	√	**x**	√	**x**
Beilin 2007 [17]	√	√	√	√	**x**	√	**x**
Boulier 2009 [18]	√	√	√	√	**x**	√	**x**
Buyse 2007 [19]	√	√	√	√	**x**	√	**x**
Camorcia 2005 [20]	√	√	√	√	**x**	√	√
Kim 2013 [22]	√	√	√	√	**x**	x	**x**
Purdie 2004 [24]	√	√	√	√	**x**	√	**x**
Sah 2006 [25]	√	√	√	√	**x**	x	√
Sia 2005 [26]	√	√	√	√	**x**	x	**x**
Velde 2007 [25]	√	√	√	√	x	x	√
For the non-**randomized trials**	Cheng 2019 [21]	Lee 2011 [23]	Zhao 2019 [26]				
Selection							
Representative of the exposed cohort	*	*	*				
Selection of the external control	*	*	*				
Ascertainment of exposure	x	x	x				
Outcome of interest not present at the start of the study	*	*	*				
Comparability							
Main factor and additional factor based on comparability of cohorts	*	*	*				
Outcome							
Assessment of outcomes	*	*	*				
Sufficient follow up time	*	*	*				
Adequacy of follow up	*	*	*				

Abbreviations: √(present), x (absent or not reported)

Table 3 Baseline features of the participants

Studies	Age (years)	Weight (kg)	Height (cm)	Gestational age (week)
	L/R	L/R	L/R	L/R
Atienzar 2008 [16]	31.0/31.0	71.0/71.0	165/162	39.6/39.4
Beilin 2007 [17]	30.0/32.0	78.0/77.0	165/163	-
Boulier 2009 [18]	28.0/27.0	75.8/74.8	165/164	39.0/39.0
Buyse 2007 [19]	27.3/26.8	77.0/76.0	166/165	39.3/39.5
Camorcia 2005 [20]	31.3/32.1	67.2/71.2	164.7/163.4	40.0/39.2
Cheng 2019 [21]	28.5/28.0	-	-	38.5/38.9
Kim 2013 [22]	32.2/33.4	66.0/68.4	161.5/164.5	39.5/40.0
Lee 2011 [23]	31.0/31.0	69.0/67.0	160/160	-
Purdie 2004 [24]	26.2/24.5	65.8/65.0	162.1/161.5	41.0/41.0
Sah 2006 [25]	27.9/26.8	83.0/80.8	166/163.6	39.7/39.8
Sia 2005 [26]	26.8/27.4	69.8/66.8	159.2/159.0	-
Velde 2007 [25]	30.2/29.9	82.0/81.0	166/167	39.4/39.5
Zhao 2019 [26]	28.0/28.4	-	-	39.7/39.6

Abbreviations: *L* Levobupivacaine, *R* Ropivacaine

Outcomes reported

The maternal outcomes which were assessed in this analysis included:

(a) Hypotension;
(b) Nausea and vomiting;
(c) Pruritus;
(d) Spontaneous vaginal delivery;
(e) Instrumental delivery;
(f) Cesarean section.

The fetal outcomes which were assessed in this analysis included:

(a) Apgar score < 7 at 1 min;
(b) Abnormality of fetal heart rate;
(c) Neonatal asphyxia. It is to be noted that newborns who required tracheal intubation and intensive care unit admission were considered in the same category as neonatal asphyxia.

The outcomes which were reported in the original studies have been listed in Table 4.

Main results of this analysis

The main results of this analysis showed that epidural ropivacaine was not associated with significantly higher risk of hypotension (RR: 0.71, 95% CI: 0.43 – 1.17; $P=0.18$) and pruritus (RR: 1.12, 95% CI: 0.89 – 1.42; $P=0.34$) when compared to levobupivacaine for labor analgesia as shown in Fig. 2. However, the risk of nausea and vomiting was significantly higher with ropivacaine (RR: 1.60, 95% CI: 1.05 – 2.44; $P=0.03$) as shown in Fig. 2.

Spontaneous vaginal delivery (RR: 0.99, 95% CI: 0.89 – 1.42; $P=0.83$), instrumental vaginal delivery (RR: 1.13, 95% CI: 0.89 – 1.45; $P=0.32$) and the risk for cesarean section (RR: 0.76, 95% CI: 0.42 – 1.37; $P=0.35$) were also not significantly different as shown in Figs. 2 and 3.

When fetal outcomes were assessed, Apgar score < 7 at 1 min (RR: 1.01: 95% CI: 0.57 – 1.80; $P=0.97$), abnormality of fetal heart rate (RR: 1.45, 95% CI: 0.55 – 3.79; $P=0.45$) and neonatal asphyxia (RR: 0.35, 95% CI: 0.10 – 1.18; $P=0.09$) were also similarly manifested as shown in Fig. 4.

The main results have been summarized in Table 5.

Sensitivity analysis and publication bias

Sensitivity analysis resulted in consistent results throughout. Excluding each study one by one and carrying out a new analysis each time did not show any result significantly different from the main result of this analysis.

Publication bias was also visually assessed and there was low evidence of publication bias among the studies that were involved in the assessment of the outcomes (Fig. 5).

Discussion

The current results showed no significant difference between epidural ropivacaine versus levobupivacaine during labor in terms of hypotension, pruritus, the number of spontaneous vaginal delivery, instrumental delivery and cesarean section. In addition, their impact on fetal outcomes was also similarly manifested.

A study based on the toxicity of ropivacaine and levobupivacaine [29] showed that in comparison to bupivacaine, both anesthetic agents were considered as 'more or well tolerated' but still they could not be considered as 'totally well tolerated' as they could still induce locally based and systemic toxicity. However, the authors in their conclusion stated that ropivacaine could be considered safest of all the currently available long acting local anesthetic agents.

Our analysis showed that ropivacaine and levobupivacaine had similar impact on Apgar score < 7 at one minute. Similarly, a review [30] showed that central blockade with these agents did not affect the Apgar score and the authors stated that an indication to use a central block during labor to reduce pain should strictly be a decision

Table 4 Endpoints which were reported in each study

Studies	Maternal outcomes	Fetal outcomes
Atienzar 2008 [16]	Hypotension, Nausea, Pruritus, spontaneous vaginal delivery, instrumental vaginal delivery, cesarean delivery	Apgar score < 7 at 1 min
Beilin 2007 [17]	Spontaneous vaginal delivery, instrumental vaginal delivery, cesarean section	Apgar score < 7 at 1 min, Apgar score < 7 at 5 min, required ventilation with mask, required tracheal intubation, required ICU admission
Boulier 2009 [18]	Spontaneous delivery, instrumental delivery, cesarean delivery	Abnormality of fetal heart rate, Apgar score < 7 at 1 min
Buyse 2007 [19]	Spontaneous delivery	Apgar score < 7 at 1 min
Camorcia 2005 [20]	Maternal hypotension, nausea/vomiting	
Cheng 2019 [21]	Cesarean section, post-dural puncture headache	Neonatal asphyxia
Kim 2013 [22]	Pruritus	Fetal bradycardia (abnormality of fetal heart rate)
Lee 2011 [23]	Spontaneous vaginal delivery, instrumental delivery, cesarean delivery, post partum hemorrhage, nausea and vomiting	Apgar Score < 8 at 1 min, frequency of newborn fever
Purdie 2004 [24]	Spontaneous delivery, instrumental delivery, cesarean section, hypotension, pruritus, nausea	
Sah 2006 [25]	Vaginal delivery, instrumental delivery, cesarean section	
Sia 2005 [26]	Hypotension, nausea and vomiting, shivering	Abnormal fetal heart rate
Velde 2007 [25]	Hypotension, pruritus, nausea, spontaneous vaginal delivery, instrumental delivery, cesarean section	Apgar score < 7 at 1 min, ICU admission
Zhao 2019 [26]	Instrumental delivery	

Abbreviations: *ICU* Intensive care unit

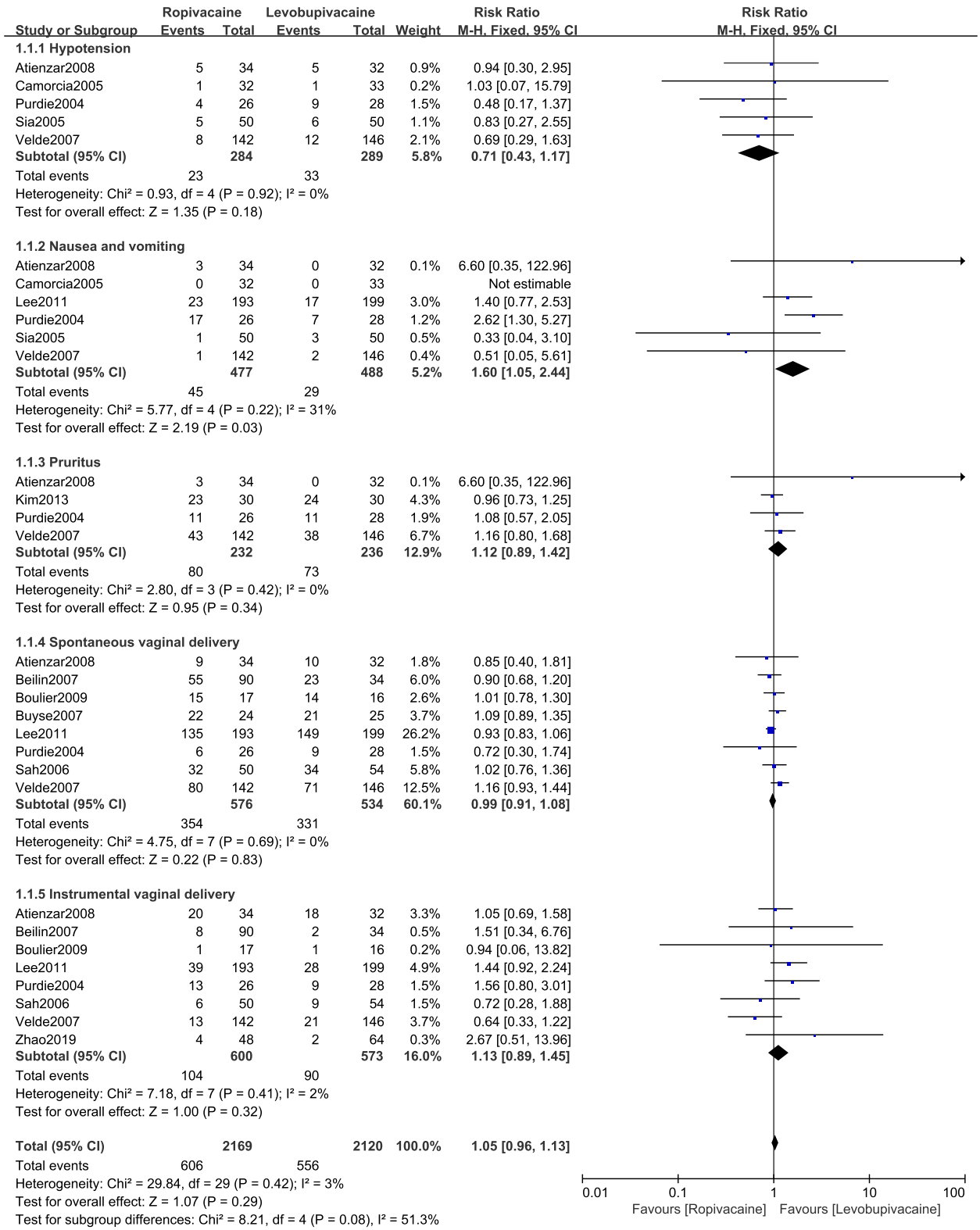

Fig. 2 Comparison maternal outcomes with Ropivacaine versus Levobupivacaine for labor analgesia

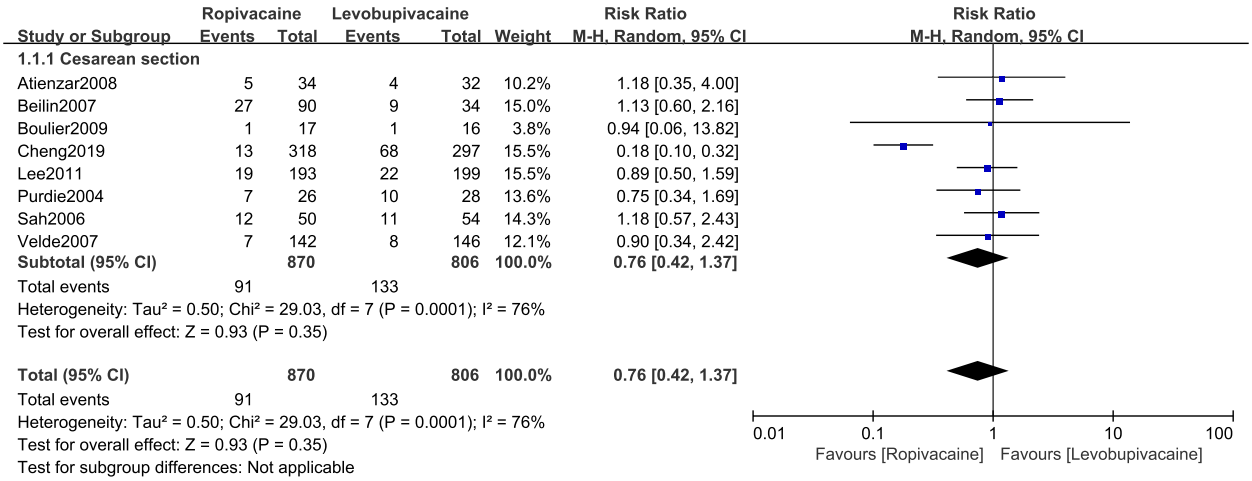

Fig. 3 Comparison of cesarean section risk with Ropivacaine versus Levobupivacaine for labor analgesia

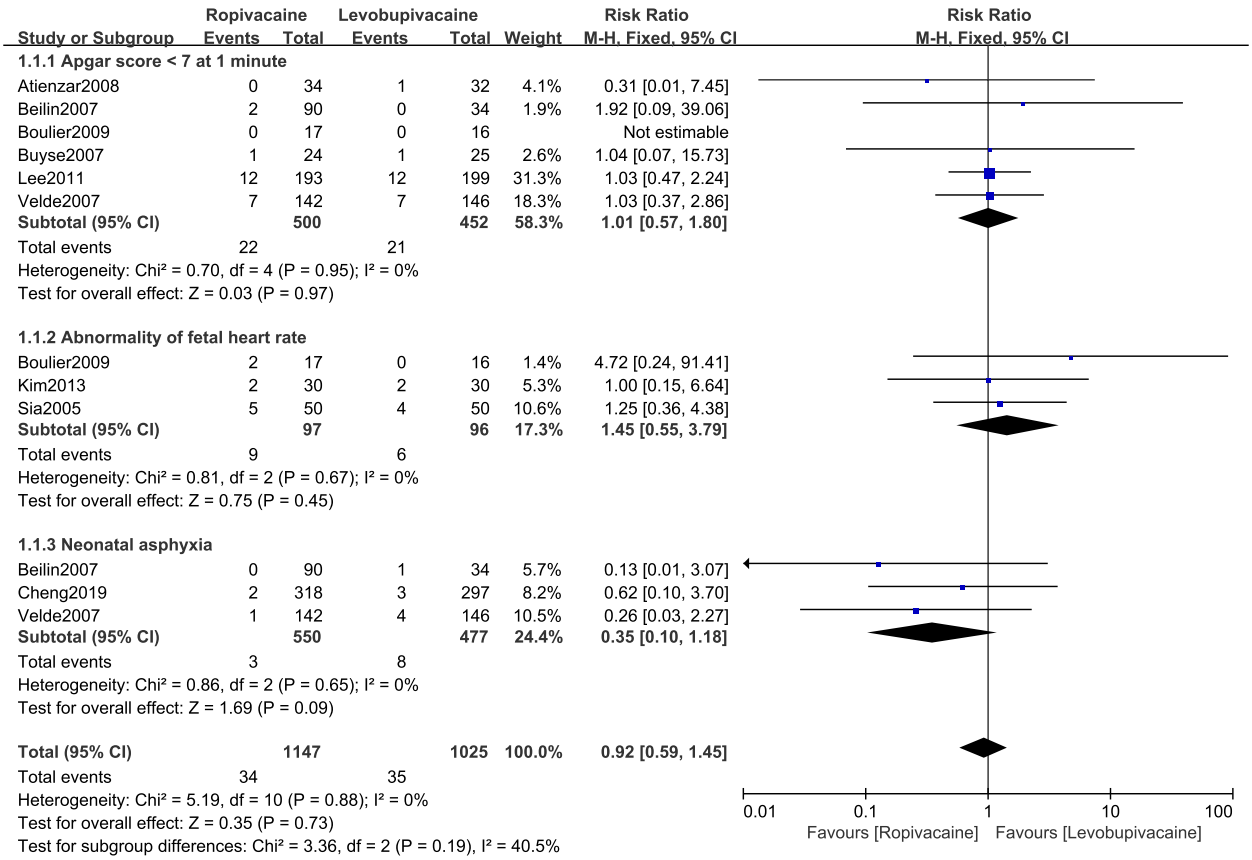

Fig. 4 Comparison of fetal outcomes based on Ropivacaine versus Levobupivacaine for labor analgesia

of the mother in labor in order to increase the patient's satisfaction.

Furthermore, another study was also in favor of this current analysis showing that when ropivacaine and levobupivacaine were compared for labor analgesia [31], both showed effective and similar outcomes without a difference in relieving pain capacity. Our analysis did not report the duration of analgesia, however, the study in current discussion showed no difference in the duration of analgesia.

Table 5 Main results of this analysis

Endpoints assessed	RR with 95% CI	*P* value	I^2 value (%)
Maternal outcomes			
Hypotension	0.71 [0.43 – 1.17]	0.18	0
Nausea and vomiting	1.60 [1.05 – 2.44]	0.03	31
Pruritus	1.12 [0.89 – 1.42]	0.34	0
Spontaneous vaginal delivery	0.99 [0.91 – 1.08]	0.83	0
Instrumental vaginal delivery	1.13 [0.89 – 1.45]	0.32	2
Cesarean section	0.76 [0.42 – 1.37]	0.35	76
Fetal outcomes			
Apgar score < 7 at 1 min	1.01 [0.57 – 1.80]	0.97	0
Abnormality of fetal heart rate	1.45 [0.55 – 3.79]	0.45	0
Neonatal asphyxia	0.35 [0.10 – 1.18]	0.09	0

Abbreviations: *RR* Risk Ratios, *CI* Confidence intervals

Another study compared bupivacaine, ropivacaine and levobupivacaine and the authors showed that there was no difference in demographic, hemodynamic and obstetric features between the participants receiving those three different anesthetic agents [32]. However, when they were ranked by potencies, a significant linear trend to increasing motor blocking potencies was observed from ropivacaine to levobupivacaine to bupivacaine.

In a meta-analysis [8] based on efficacy and safety of local anesthetics including bupivacaine, ropivacaine and levobupivacaine in combination with sufentanil in epidural anesthesia for labor and delivery including data of 1506 participants which have been utilized, the authors showed a significantly longer labor analgesia to have been achieved with ropivacaine and levobupivacaine, with the former being associated with lesser motor blockade, while bupivacaine was associated with a shorter labor duration after epidural analgesia with a beneficial effect of lower incidence of instrumental delivery. In addition, a randomized clinical trial including 450 nulliparous parturients showed lower concentration of ropivacaine, bupivacaine and levobupivacaine to produce similar analgesic effect, motor blockade and safety for labor analgesia [33].

Limitations

This study also has limitations. First of all, due to the low number of participants assigned to each group, the results of this analysis might not be as robust as expected. If more studies would have been available with a higher number of participants, there could be slight changes in the results. Secondly, data from randomized trials and observational studies were mixed during analysis and this could contribute to the increased heterogeneity when assessing certain outcomes. The different dosages, the concentration of the anesthetic agents, the different techniques which were used could have an impact on

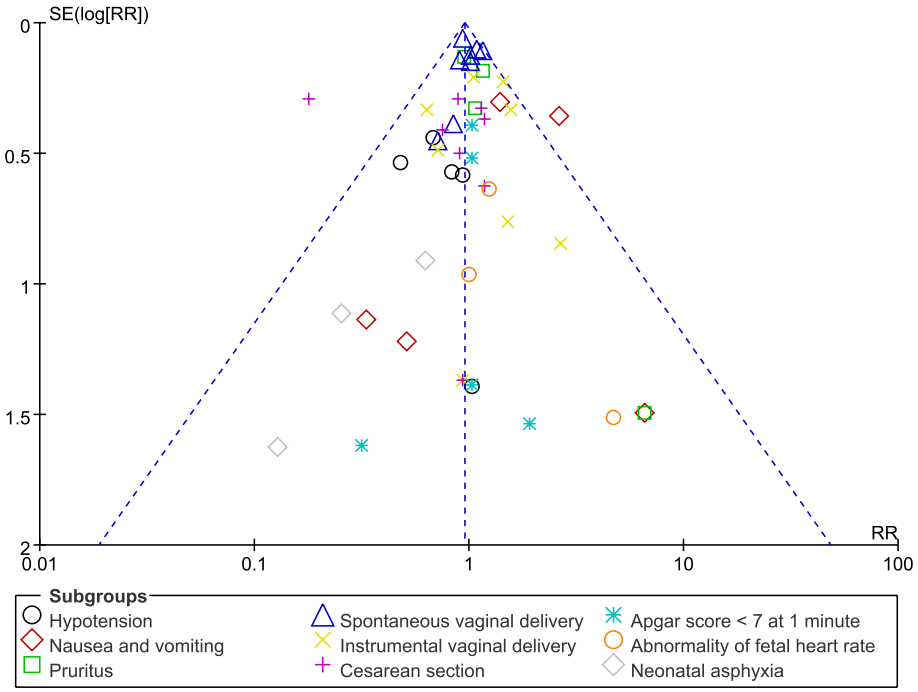

Fig. 5 Funnel plot showing publication bias

the results. A higher dosage and concentration of anesthetic agent could increase nausea and vomiting and could be associated with other complications whereas better techniques could minimize the risks of complications. Another limitation could be the fact that when assessing for Apgar score less than 7 at 1 min, data from a study which reported Apgar score less than 8 at 1 min were included altogether and assessed. This could also be a minor limitation. In addition, in our study, the dosage of medication was ignored. The fact that drug dosage was ignored in the study could affect the outcome of this analysis and this could be considered as another limitation. Also, this study did not assess the impact of such epidural anesthesia on timing of surgery. A trial sequential analysis [34] which could have provided robustness of this meta-analysis findings and the need for further research was not carried out. This could be another limitation.

Conclusion

To conclude, our analysis showed both epidural ropivacaine and levobupivacaine to be equally effective for labor analgesia in terms of maternal and fetal outcomes. No major adverse maternal and fetal outcome was observed in this analysis. However, considering the several limitations of this analysis, further larger studies should be able to solve and clarify this issue.

Acknowledgements
Not applicable.

Authors' contributions
The authors Zhen Li, Xinxing Zhou and Hailin Wang were responsible for the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the initial manuscript and revising it critically for important intellectual content. The final draft was written by the authors Zhen Li and Xinxing Zhou. All the authors gave their approval to the final manuscript as it has been written.

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Data availability
Data which have been used in this study can freely be accessed and are included in the original published articles. References of the original papers involving the data source which have been used in this paper have been listed in the main text of this current manuscript. All data are publicly available in electronic databases.

Declarations

Ethics approval and consent to participate
Ethical approval and consent to participate were not applicable for this systematic review and meta-analysis.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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