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Original Article

Efficacy of epidural analgesia with ropivacaine on labor, maternal, and neonatal: a meta-analysis of prospective and retrospective studies

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Abstract: Background: Epidural analgesia is generally accepted as the most effective method for pain relief during labor. However, results of published studies regarding the efficacy of epidural analgesia with ropivacaine on the modes of delivery, labor progression, need for oxytocin, maternal and neonatal outcomes are inconsistent. Objective: We conducted a comprehensive meta-analysis to appraise the efficacy and security of ropivacaine epidural analgesia on labor, maternal and neonatal. Methods: Databases of the PubMed, Embase, and Cochrane Library were searched independently by 2 reviewers to retrieve eligible studies that compare the influence of ropivacaine epidural analgesia (REA) on labor, maternal and neonatal with non-epidural analgesia (NEA) in parturients. Primary outcomes were the modes of labor, duration of labor and the need for oxytocin, and secondary outcomes were maternal outcomes (pain scores, nausea, vomiting and pruritus), and neonatal outcomes (Apgar scores, umbilical artery pH). Standardised mean difference (SMD) or odds ratio (OR) with their 95% confidence intervals (CIs) were calculated by fixed- or random-effects models, depending upon the heterogeneity of the included trials. Sensitivity analyses and subgroup analyses were also performed. Newcastle-Ottawa Scale (NOS) was applied to assess the qualities of all included studies. Results: A total of eight studies (four prospective and four retrospective studies) with ten trials involving 18832 parturients were included in this analysis. Comparing with the NEA, the rate of spontaneous vaginal delivery was decreased, the risk of instrumental delivery was increased, and the second stage of labor was prolonged in the REA group (OR 0.61, 95% CI 0.43-0.87, P=0.006, I^2=84%; OR 2.2, 95% CI 1.93-2.54, P=0.000, I^2=13%; SMD 0.58, 95% CI 0.41-0.75, P=0.000, I^2=89%, respectively). There were no statistical differences of the rate of cesarean delivery (OR 1.26, 95% CI 0.82-1.96, P=0.296, I^2=83%), the need for oxytocin (OR 1.43, 95% CI 0.95-2.13, P=0.09, I^2=95%), and the first stage of labor (SMD 0.27, 95% CI -0.40-0.93, P=0.427, I^2=99%) between two groups. Pain scores were significantly lower in parturients receiving epidural ropivacaine when comparing to those with non-epidural method of relieving pain or those with no any way for pain relief in labour. No differences concerning maternal outcomes (nausea, vomiting and pruritus) and neonatal adverse events (Apgar scores, umbilical artery pH) were observed. Conclusions: This meta-analysis shows that REA increases the rate of instrumental delivery and the duration of the second stage of labor, and decreases rate of spontaneous vaginal delivery. However, REA does not affect the rate of cesarean delivery, the need for oxytocin and the first stage of labor. However, all the results should be interpreted cautiously, as heterogeneous data are used for analyzing.

Keywords: Epidural analgesia, ropivacaine, labor, meta-analysis

Introduction

Epidural analgesia (EDA) was firstly used in obstetric practice in 1946 and its use in labour has steadily increased until the last decade [1]. Approximately 20% of parturients in the UK and 58% of parturients in the USA receive this therapy for pain relief [2, 3]. EDA is a central nerve blockade technique, which involves injection of local anaesthetics into the lower region of the spine closely to the nerves that transmit painful stimuli from the contracting uterus and birth canal. The anaesthetics inhibit nerve conduction by blocking sodium channels in nerve membranes, thereby preventing propagation of nerve impulses along these fibres.

EDA is today the optimized analgesic method for parturients in labour and considered effective and well tolerated [4]. However, controversy

exists as to effect of epidurals on the progress of labour, mode of delivery and effect on the maternal and neonatal. Most previous studies have demonstrated that EDA was associated with a longer second stage of labor and a higher rate of operative vaginal delivery compared with labor without analgesia [5-8]. Besides, some studies have shown that parturients who were administered EDA were more likely to have a caesarean delivery for dystocia and fetal distress [5, 7], whereas other studies have reported that EDA did not affect the caesarean delivery rate [1, 9]. In addition, effect of EDA on the neonate may be mixed. Higher cord pH values and less naloxone use at birth have been reported [10]. The aim of this meta-analysis is to assess the effectiveness of epidural analgesia with ropivacaine and the risk of potential adverse effects when compared with non-epidural methods of relieving pain in labour or no pain relief.

Materials and methods

Literature search

To identify the studies of interest, we conducted a computerized literature search by two reviewers. Literature sources included the PubMed, Embase, and the Cochrane Library databases with date from 2000 to 2015. Search terms included: “epidural anesthesia” or “epidural” or “intravertebral anesthesia”, and “delivery” or “childbirth” or “parturition” or “labor” or “give birth to” or “accouchement” or “partus”. Literature search was not limited study design. The title and abstract of studies identified in the computerized search were scanned to exclude any studies that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. Additionally, we also manually searched the reference lists of review papers and every publication retrieved to find any additional relevant articles.

Study selection

The studies included in our meta-analysis should meet the following criteria: (1) they were either prospective or retrospective studies; (2) the efficacy of ropivacaine epidural analgesia (REA) on labor (mode of delivery and labor stage), maternal outcomes (nausea, vomiting and pruritus), and neonatal outcomes (Apgar scores, umbilical artery pH) were used to compare with that of non-epidural analgesia (NEA) in parturients; (3) studies contained sufficient data to calculate SMD or OR with their 95% CIs. Review, meta-analyses and the studies did not provide sufficient data were excluded. Study selection was made independently by two reviewers and any queries or discrepancies were resolved by consensus or by discussion with a third reviewer.

Quality assessment

The quality of included studies was assessed by two experienced reviewers independently and any discrepancies were subsequently resolved by consultation. The Newcastle-Ottawa Scale was used to evaluate the quality of each study [11]. This scale assessed the quality of includes studies in three aspects, including the selection of the study groups, the comparability of the groups, and ascertainment of outcome of interest.

Data extraction

Two experienced investigators independently performed the data extraction. Any discrepancies between the extracted data were solved by consensus. If the disagreements continued after discussion they were resolved by negotiating with another reviewer. The following information was recorded: first author’s last name, year of publication, design of the study, number of parturients, age, primary end outcomes (the modes of labor, duration of labor and the need for oxytocin), the secondary end outcomes (pain scores, nausea, vomiting, pruritus, Apgar scores, umbilical artery pH), inclusion criteria and exclusion criteria for parturients, if applicable.

Statistical analysis

All data pertaining to the predetermined outcome measures were transcribed to STATA version 12.0 for meta-analysis (STATA 12.0: Stata Corporation, College Station, Texas, USA). Subgroup analysis was conducted according to study type _ (prospective *vs* retrospective study). Continuous variables were pooled as SMD with its 95% CI, while dichotomous data were pooled as OR with its 95% CI; if meta-analytic synthesis was not possible, the data were simply presented qualitatively [12].

Table 1. Basic characteristics of the trials included in the meta-analysis

Study	Design	Parity	Group	Number (n)	Age (yr)	Inclusion criteria	Exclusion criteria	Analgesia regimens	Quality*
Decca et al, 2004	Retrospective study	Mixed	Epidural	207	32.9±3.9	NA	NA	Test dose: lidocaine (2%) 2-4 ml; Initial bolus: ropivacaine (0.1-0.15%) 15 ml + sufentanil (2 ug/ml) 5 ml; PCEA: ropivacaine (0.1-0.15%) 10 ml, lock-out time 60-90 min	6
			Non-epidural	414	NA			None	
Andrea et al, 2007 (1)	Retrospective study	Nulliparous	Epidural	150	27.9±5.6	Parturient who got an EDA only for the reason of decreasing labour pain	Parturient with contraindication for EDA and factor that could influence the mode of delivery	Test dose: bupivacaine (0.5%); Initial bolus: ropivacaine (0.2%) 15-20 ml; ropivacaine (0.2%) upon request	6
			Non-epidural	133	28.1±5.3			None	
Andrea et al, 2007 (2)	Retrospective study	Multiparous	Epidural	32	31.6±2.5			Test dose: bupivacaine (0.5%); Initial bolus: ropivacaine (0.2%) 15-20 ml; ropivacaine (0.2%) upon request	
			Non-epidural	215	30.6±5.1			None	
Douma et al, 2011	Prospective study	Mixed	Epidural	10	31.0±5.2	ASA I or II; active labour; singleton; cephalic presentation; without prior use of opioid analgesics	Cervical dilation >5 cm; preeclampsia; insulin-dependent diabetes; substance abuse; opioid allergy; morbid obesity	Initial bolus: ropivacaine (0.2%) 12.5 ml; Continuous infusion: ropivacaine (0.1%) + sufentanil (0.5 ug/ml), 10 ml/h	7
			Non-epidural	10	32.7±5.9			Initial bolus: sufentanil 40 ug; PCIA: sufentanil 40 ug, lock-out time 2 min	
Tveit et al, 2012	Prospective study	Mixed	Epidural	20	27	ASA I or II; singleton; cervical dilatation >2 cm; normal fetal; no complications during pregnancy; gestation age 37-40 weeks	Women requested EDA; received pethidine less than 8 h before the study period; there were contraindications to remifentanil	Initial bolus: ropivacaine (1 mg/ml) + fentanyl (2 ug/ml), 15 ml; Continuous infusion: ropivacaine (1 mg/ml) + fentanyl (2 ug/ml), 10 ml/h	7
			Non-epidural	17	26			Initial bolus: ropivacaine 0.15 ug/Kg; Continuous infusion: ropivacaine (50 ug/ml), 2 ml/min	
Ding et al, 2014	Prospective study	Nulliparous	Epidural	107	29±3	Nulliparas; at term; singleton; cephalic; preparing to deliver vaginally	History of psychiatric disease; obesity (body weight ≥100 kg); presence of epidural labor analgesia contraindications	Initial bolus: ropivacaine (0.1%) + fentanyl (0.5 ug/ml), 10 ml; PCEA: ropivacaine (0.08%) + fentanyl (0.4 ug/ml), 6 ml, lock-out time 15 min	6
			Non-epidural	107	29±3			None	
Agrawal et al, 2014	Prospective study	Nulliparous	Epidural	60	28.1±3.8	Nulliparity; age 20-35 y; body weight <80 kg; gestation ≥36 wk; single fetus; vertex presentation; cervical dilatation ≥4 cm	Multiparity; cephalopelvic disproportion; cervical dilatation ≤4 cm; medical complications; contraindications for epidural analgesia	Test dose: lidocaine (2%) 3 ml; Initial bolus: ropivacaine (0.2%) 10 ml + fentanyl (50 ug); Continuous infusion: ropivacaine (0.1%) + fentanyl (2 ug/ml), 10 ml/h	7
			Non-epidural	60	26.9±3.8			None	
Lin et al, 2014	Retrospective study	Nulliparous	Epidural	247	29.3±3.1	ASA I or II; primipara; singleton; cephalic presentation; gestational Age >36 wk	Parturient with request for caesarean section or stillbirth	Initial bolus: ropivacaine (0.068%) + sufentanil (0.3 ug/ml), 10 ml; Continuous infusion: ropivacaine (0.068%) + sufentanil (0.3 ug/ml), 8 ml/h; PCEA: ropivacaine (0.08%) + fentanyl (0.4 ug/ml), 5 ml, lock-out time 15 min	6
			Non-epidural	191	29.6±3.2			Initial bolus: remifentanil 0.4 ug/Kg; PCIA: remifentanil 0.04-0.05 ug/Kg/min, lock-out time 5 min	

Huang et al, 2015 (1)	Retrospective study	Nulliparous	Epidural	7260	NA	Deliveries after 37 weeks of gestation	Multiple gestations; fetal anomalies or demise; placenta previa; ephalopelvic disproportion; active genital herpes or condylomatous infection	Initial bolus: ropivacaine (1 mg/ml) + fentanyl (7.5 ug/ml), 10 ml; Continuous infusion: ropivacaine (0.8 mg/ml) + fentanyl (2 ug/ml), 10 ml/h	5
			Non-epidural	2915				None	
Huang et al, 2015 (2)	Retrospective study	Multiparous	Epidural	2987				Initial bolus: ropivacaine (1 mg/ml) + fentanyl (7.5 ug/ml), 10 ml; Continuous infusion: ropivacaine (0.8 mg/ml) + fentanyl (2 ug/ml), 10 ml/h	
			Non-epidural	3690				None	

*Evaluated by the 9-star Newcastle-Ottawa Scale. NA=Not available, PCEA=Patient-controlled epidural analgesia, PCIA=Patient-controlled intravenous analgesia. Andrea et al, 2007-contains two studies (Andrea et al, 2007 (1) and Andrea et al, 2007 (2)); Huang et al, 2015-contains two studies (Huang et al, 2015 (1) and Huang et al, 2015 (2)).

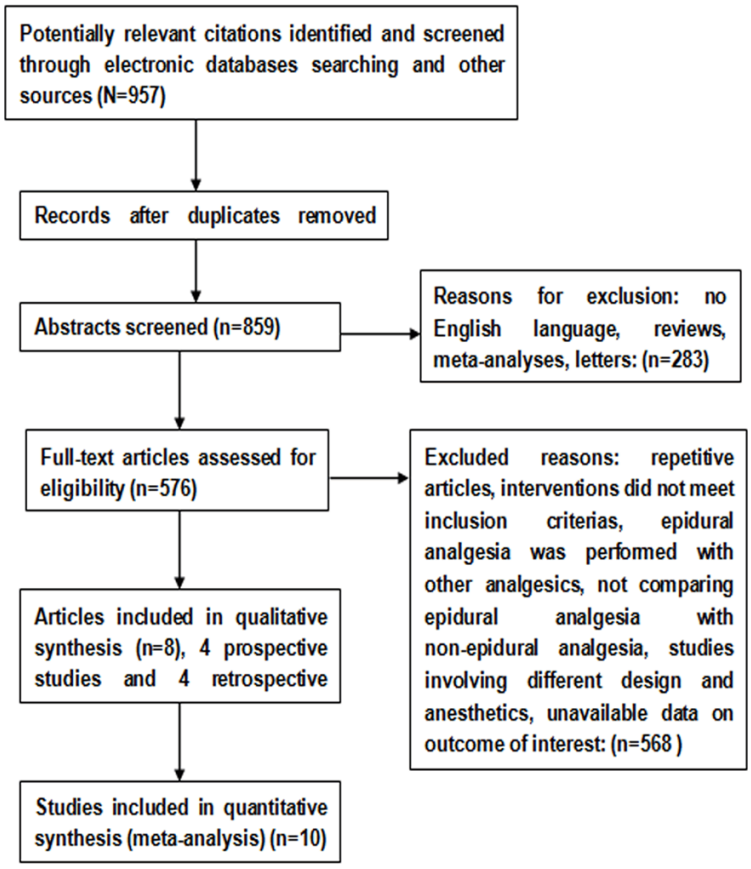


Figure 1. Flow chart showing study selection procedure.

Presence and possible causes of between-study heterogeneity was evaluated by Cochrane's Q test [13]. We also calculated the quantity I^2 that describes the percent variation across included studies and that is as a result of heterogeneity rather than chance; it was considered to be heterogeneous if $P<0.1$ or $I^2>50\%$ [14]. The fixed effects model was adopted if there was no heterogeneity among studies, otherwise, the random effects model was used.

To evaluate stability of the results and explore heterogeneity, we performed a one-way sensitivity analysis. The scope of this analysis was to evaluate the influence of each study on overall combined SMDs or ORs, by removing one study at a time [15]. Finally, publication bias was assessed by a visual inspection of the funnel plot, and also by Begg and Egger's tests [16, 17]. The underlying notion is that small studies are unlikely to be published but generally having larger standard errors. If the funnel plot showed an asymmetry, it suggested that studies that reported negative results might not have been published [18]. All *p*-values were two-tailed and less than 0.05 suggesting statistically significant.

Results

Search results and description of the studies

A total 957 reports were initially identified by primary computerized literature search. However, after scanning titles and abstracts, 381 studies were excluded because they were laboratory studies, reviews, meta-analyses, letters, or irrelevant to the current study. We retrieved 576 potentially relevant papers for further review. The full texts were read, and reference lists were checked. Finally, 8 studies (4 prospective and 4 retrospective studies) including 18832 parturients were included in this analysis that evaluating the efficacy of REA on labor, maternal, and neonatal outcomes [19-26]. The included studies were published between 2004 and 2015. Characteristics of these studies were presented in **Table 1** (Andrea et al, 2007-contains two trials (Andrea et al, 2007 (1) and Andrea et al, 2007 (2)), Huang et al, 2015-contains two trials (Huang et al, 2015 (1) and Huang et al, 2015 (2))), and the search flow diagram was presented in **Figure 1**.

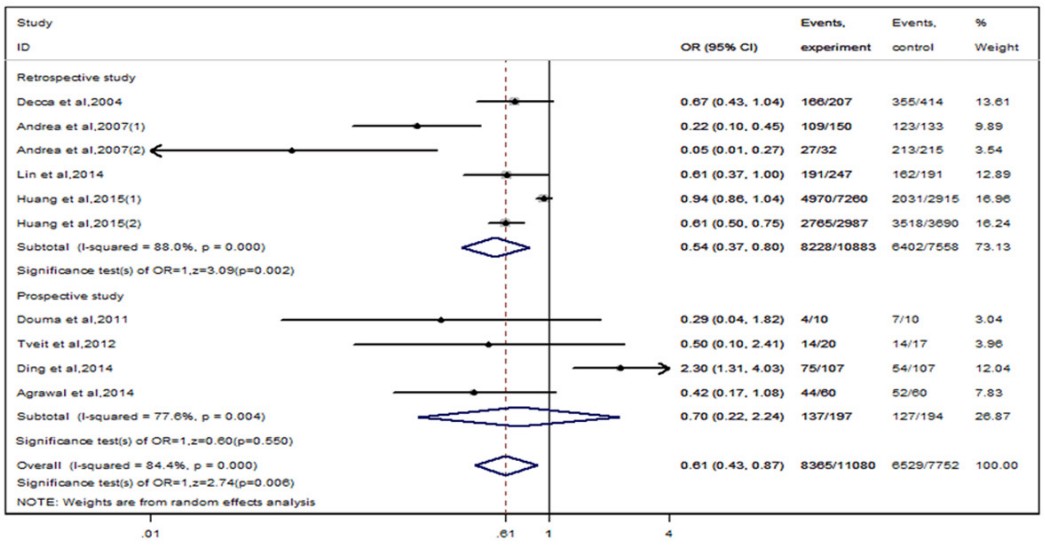
Methodological quality assessment

The qualities of all included studies were assessed by NOS, and results were shown in **Table 1**. Scores ranged from 5 to 7.

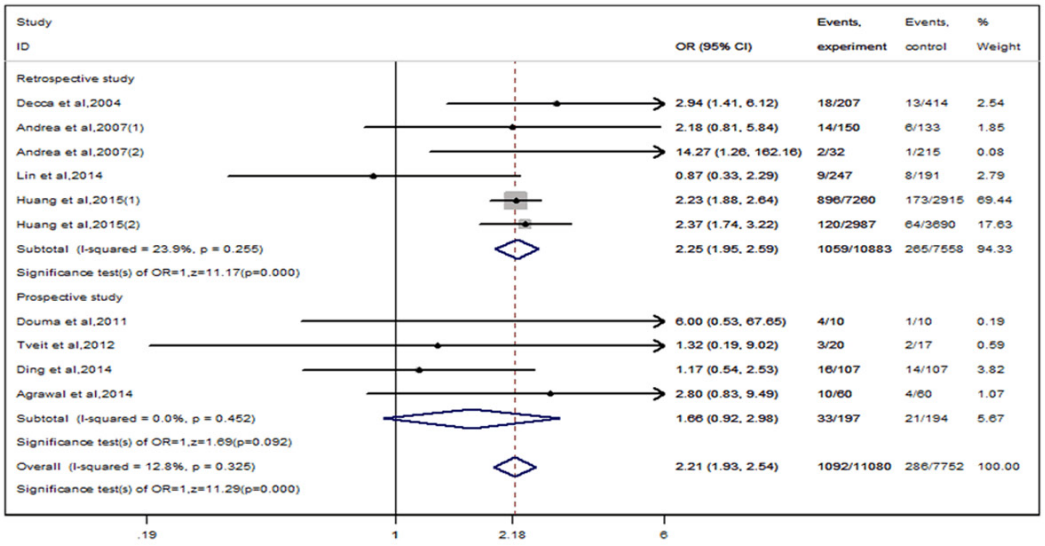
Quantitative data synthesis

Association between REA and spontaneous vaginal delivery (SVD): Eight studies reported data on the SVD. Significant heterogeneity was found ($P<0.001$), so random-effects model was used to calculate the combined OR and 95% CI.

A


Study
ID
OR (95% CI)
Events, experiment
Events, control
% Weight
Retrospective study
Decca et al,2004 0.67 (0.43, 1.04) 166/207 355/414 13.61
Andrea et al,2007(1) 0.22 (0.10, 0.45) 109/150 123/133 9.89
Andrea et al,2007(2) 0.05 (0.01, 0.27) 27/32 213/215 3.54
Lin et al,2014 0.61 (0.37, 1.00) 191/247 162/191 12.89
Huang et al,2015(1) 0.94 (0.86, 1.04) 4970/7260 2031/2915 16.96
Huang et al,2015(2) 0.61 (0.50, 0.75) 2765/2987 3518/3690 16.24
Subtotal (I-squared = 88.0%, p = 0.000) 0.54 (0.37, 0.80) 8228/10883 6402/7558 73.13
Significance test(s) of OR=1,z=3.09(p=0.002)
Prospective study
Douma et al,2011 0.29 (0.04, 1.82) 4/10 7/10 3.04
Tveit et al,2012 0.50 (0.10, 2.41) 14/20 14/17 3.96
Ding et al,2014 2.30 (1.31, 4.03) 75/107 54/107 12.04
Agrawal et al,2014 0.42 (0.17, 1.08) 44/60 52/60 7.83
Subtotal (I-squared = 77.6%, p = 0.004) 0.70 (0.22, 2.24) 137/197 127/194 26.87
Significance test(s) of OR=1,z=0.60(p=0.550)
Overall (I-squared = 84.4%, p = 0.000) 0.61 (0.43, 0.87) 8365/11080 6529/7752 100.00
Significance test(s) of OR=1,z=2.74(p=0.006)
NOTE: Weights are from random effects analysis
.01
.61
1
4

B


Study
ID
OR (95% CI)
Events, experiment
Events, control
% Weight
Retrospective study
Decca et al,2004 2.94 (1.41, 6.12) 18/207 13/414 2.54
Andrea et al,2007(1) 2.18 (0.81, 5.84) 14/150 6/133 1.85
Andrea et al,2007(2) 14.27 (1.26, 162.16) 2/32 1/215 0.08
Lin et al,2014 0.87 (0.33, 2.29) 9/247 8/191 2.79
Huang et al,2015(1) 2.23 (1.88, 2.64) 896/7260 173/2915 69.44
Huang et al,2015(2) 2.37 (1.74, 3.22) 120/2987 64/3690 17.63
Subtotal (I-squared = 23.9%, p = 0.255) 2.25 (1.95, 2.59) 1059/10883 265/7558 94.33
Significance test(s) of OR=1,z=11.17(p=0.000)
Prospective study
Douma et al,2011 6.00 (0.53, 67.65) 4/10 1/10 0.19
Tveit et al,2012 1.32 (0.19, 9.02) 3/20 2/17 0.59
Ding et al,2014 1.17 (0.54, 2.53) 16/107 14/107 3.82
Agrawal et al,2014 2.80 (0.83, 9.49) 10/60 4/60 1.07
Subtotal (I-squared = 0.0%, p = 0.452) 1.66 (0.92, 2.98) 33/197 21/194 5.67
Significance test(s) of OR=1,z=1.69(p=0.092)
Overall (I-squared = 12.8%, p = 0.325) 2.21 (1.93, 2.54) 1092/11080 286/7752 100.00
Significance test(s) of OR=1,z=11.29(p=0.000)
.19
1
2.18
6

C

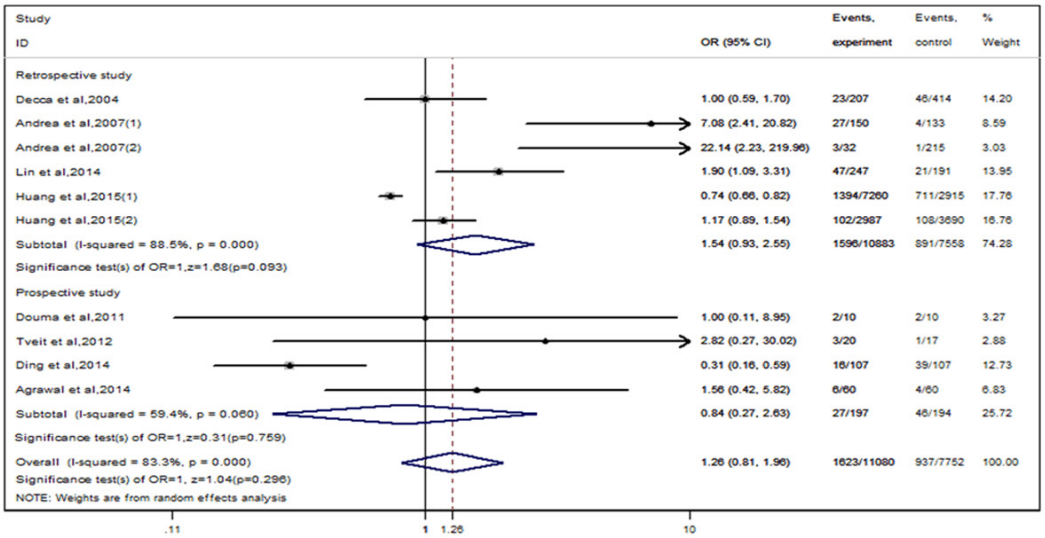

Study
ID
OR (95% CI)
Events, experiment
Events, control
% Weight
Retrospective study
Decca et al,2004 1.00 (0.59, 1.70) 23/207 46/414 14.20
Andrea et al,2007(1) 7.08 (2.41, 20.82) 27/150 4/133 8.59
Andrea et al,2007(2) 22.14 (2.23, 219.96) 3/32 1/215 3.03
Lin et al,2014 1.90 (1.09, 3.31) 47/247 21/191 13.95
Huang et al,2015(1) 0.74 (0.66, 0.82) 1394/7260 711/2915 17.76
Huang et al,2015(2) 1.17 (0.89, 1.54) 102/2987 108/3690 16.76
Subtotal (I-squared = 88.5%, p = 0.000) 1.54 (0.93, 2.55) 1596/10883 891/7558 74.28
Significance test(s) of OR=1,z=1.68(p=0.093)
Prospective study
Douma et al,2011 1.00 (0.11, 8.95) 2/10 2/10 3.27
Tveit et al,2012 2.82 (0.27, 30.02) 3/20 1/17 2.88
Ding et al,2014 0.31 (0.16, 0.59) 16/107 39/107 12.73
Agrawal et al,2014 1.56 (0.42, 5.82) 6/60 4/60 6.83
Subtotal (I-squared = 59.4%, p = 0.060) 0.84 (0.27, 2.63) 27/197 46/194 25.72
Significance test(s) of OR=1,z=0.31(p=0.759)
Overall (I-squared = 83.3%, p = 0.000) 1.26 (0.81, 1.96) 1623/11080 937/7752 100.00
Significance test(s) of OR=1, z=1.04(p=0.296)
NOTE: Weights are from random effects analysis
.11
1
1.26
10

Figure 2. Forest plots of delivery outcomes. A. Rate of spontaneous vaginal deliveries. B. Rate of instrumental deliveries. C. Rate of cesarean deliveries. 95% CI=95% confidence interval.

The pooled results demonstrated that the rate of SVD was higher in NEA group in comparison with REA group (OR 0.61, 95% CI 0.43-0.87, *P*=0.000). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the rate of SVD in prospective studies (OR 0.70, 95% CI 0.22-2.24, *P*=0.550), but statistical difference in retrospective studies (OR 0.540, 95% CI 0.37-0.80, *P*=0.002 (**Figure 2A**).

Association between REA and instrumental delivery (ID): Eight studies reported data on the ID. No apparent heterogeneity was detected (*P*=0.325), so fixed-effects model was used. The combined result suggested that the rate of ID was higher in REA group in comparison with NEA group (OR 2.21, 95% CI 1.93-2.54, *P*= 0.000). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the rate of ID among prospective studies (OR 1.66, 95% CI 0.92-2.98, *P*=0.092), but difference among retrospective studies (OR 2.25, 95% CI 1.95-2.59, *P*=0.004) (**Figure 2B**).

Association between REA and cesarean delivery (CD): Eight studies reported data on the CD. Significant heterogeneity was found (*P*=0.000), so random-effects model was used. The pooled results demonstrated that there was no association between the use of REA and the rate of CD (OR 1.26, 95% CI 0.82-1.96, *P*=0.296). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the rate of CD neither among prospective studies (OR 0.84, 95% CI 0.27-2.63, *P*=0.759) , nor among retrospective studies (OR 1.54, 95% CI 0.93-2.56, *P*= 0.093) (**Figure 2C**).

Association between REA and the duration of the first stage of labor (DFSL): Five trials reported by four studies provided data on the DFSL [21, 22, 24, 26]. Significant heterogeneity was found (*P*=0.000), so random-effects model was used to calculate the combined SMD and 95% CI. The pooled results demonstrated that there was no association between the use of REA and the DFSL (SMD 0.27, 95% CI -0.39-0.93, *P*=0.427). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the DFSL neither among prospective studies (SMD -0.28, 95% CI -0.58-0.01, *P*=0.058), nor among retrospective studies (SMD 0.91, 95% CI -0.06-1.88, *P*=0.067) (**Figure 3A**).

Association between REA and the duration of the second stage of labor (DSSL): Five trials in four studies reported data on the DSSL [21, 22, 24, 26]. Significant heterogeneity was found (*P*=0.000), so random-effects model was used. The combined results suggested that the DSSL was prolonged in REA group in comparison with NEA group (SMD 0.58, 95% CI 0.41-0.75, *P*= 0.000). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the DSSL among prospective studies (SMD -0.33, 95% CI -1.24-0.58, *P*=0.478), but found difference among retrospective studies (SMD 0.75, 95% CI 0.66-0.84, *P*=0.000) (**Figure 3B**).

Association between REA and oxytocin augmentation (OA): Seven trials in six studies reported data on the OA [19, 21-23, 25, 26]. Significant heterogeneity was found (*P*=0.000), so random-effects model was used to calculate the combined OR and 95% CI. The pooled results demonstrated that there was no association between the use of REA and the rate of OA (OR 1.42, 95% CI 0.95-2.13, *P*=0.090). After stratifying the data into subgroups on the basis of study design, we found no association between the use of REA and the rate of OA neither among prospective studies (OR 1.07, 95% CI 0.23-5.05, *P*=0.928), nor among retrospective studies (OR 1.42, 95% CI 0.90-2.25, *P*=0.137) (**Figure 4**).

Qualitative description of maternal and neonatal outcomes

Pain scores were significantly lower in parturients receiving REA group when comparing to NEA group. However, the definition and assessment of this variable was inconsistent among the trials [20-23, 25].

The incidence nausea, vomiting, and pruritus among parturients with REA group and NEA group were compared and reported by three

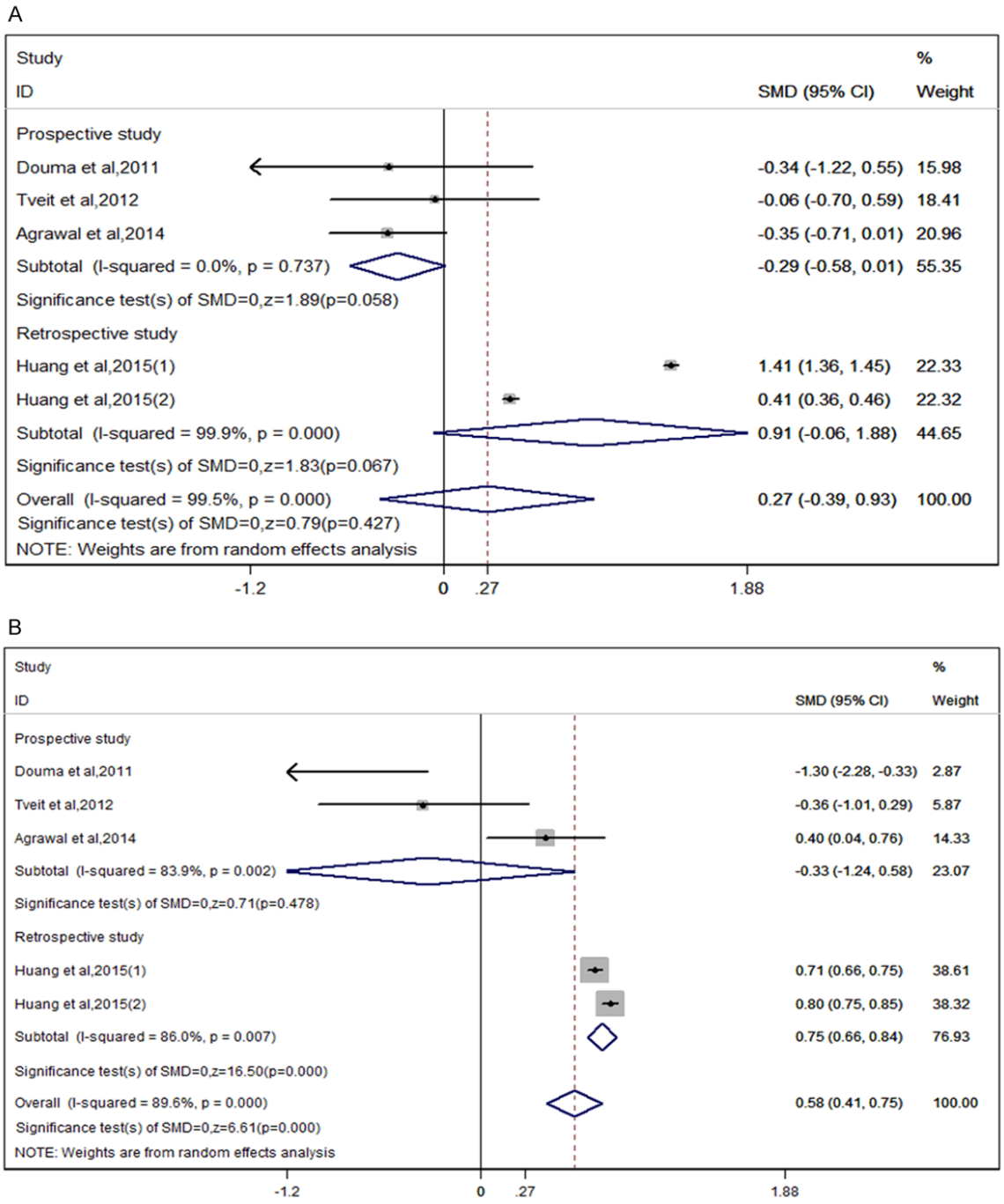


Figure 3. Forest plots of duration of labor. A. Duration of the first stage of labor (minutes). B. Duration of the second stage of labor (minutes). 95% CI=95% confidence interval.

studies [21, 22, 25]. No trial reported a difference between two groups.

Apgar scores at 1 min and 5 min, and umbilical artery pH were reported [19, 21-23, 25, 26]; however, these data were not appropriate for synthesis. Actually, there was no statistically difference between the groups with respect to these outcomes.

Sensitivity analysis

The source of heterogeneity was assessed by sensitivity analysis, and sustantial heterogene-

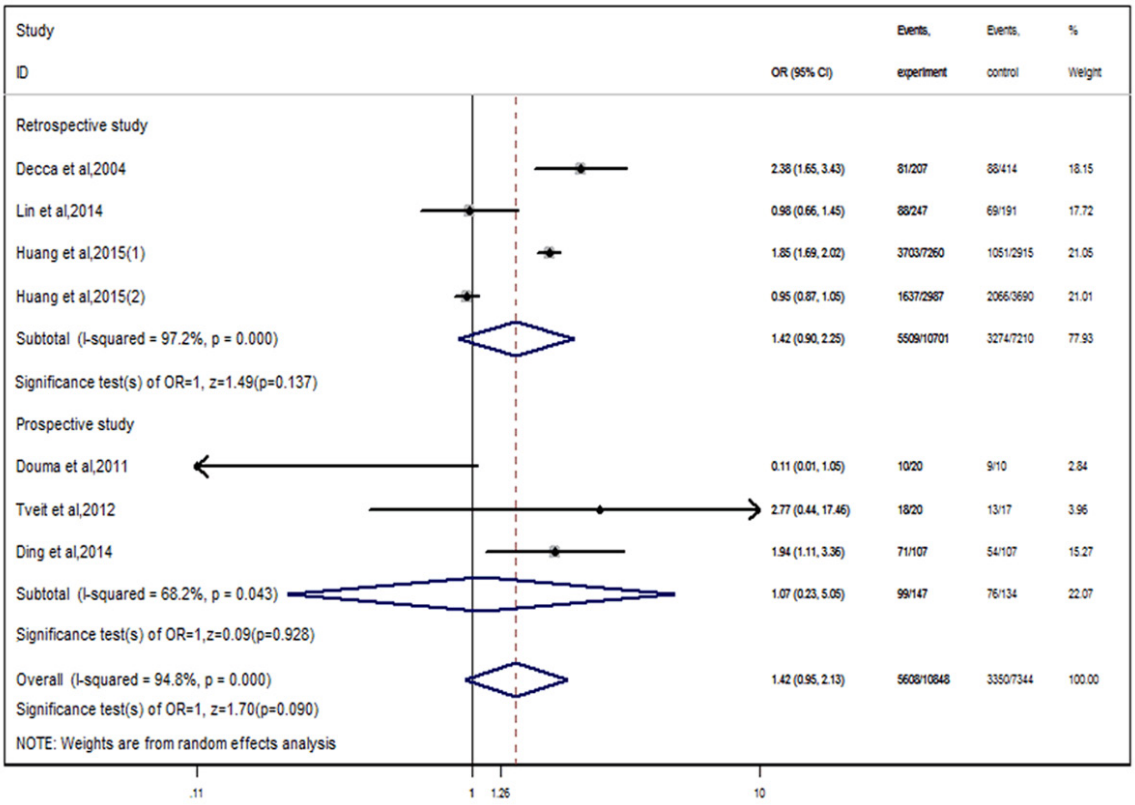


Figure 4. Forest plot of the rate of patients requiring oxytocin. 95% CI=95% confidence interval.

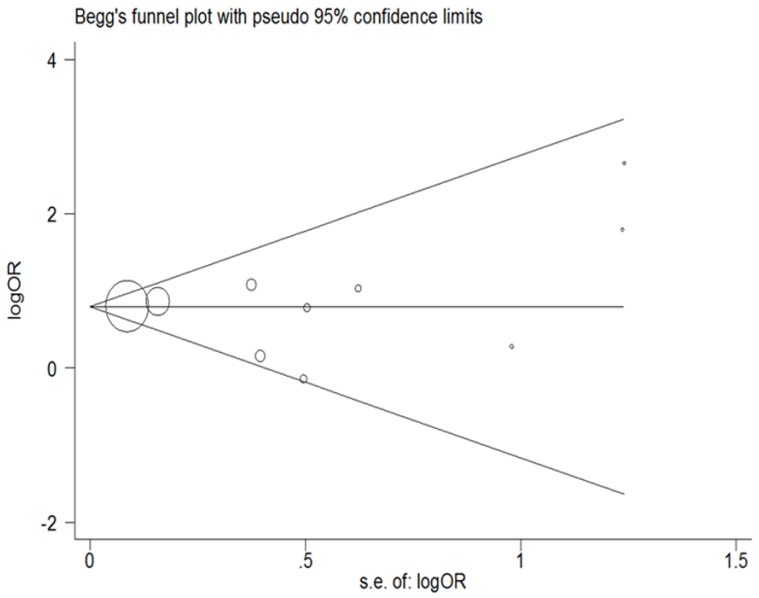


Figure 5. Begg's funnel plot of publication bias test. Each point represents a separate study for the indicated association. Log (*OR*), natural logarithm of OR. *Horizontal line*, mean effect size.

ity was detected for all primary end outcomes except for the rate of instrumental delivery. We found that the trial reported by Huang et al [26] was the source of heterogeneity.

Publication bias

We examined publication bias through graphical inspection and quantitative evaluation. Except for the duration of the second stage of labor (Begg's test P=0.086; Egger's test P=0.025), neither Begg's funnel plot nor Egger's test demonstrated the presence of publication bias in spontaneous vaginal delivery (Begg's test P=0.592; Egger's test P=0.097), instrumental delivery (Begg's test P=0.371; Egger's test P=0.978), cesarean delivery (Begg's test P=0.474; Egger's test, P=0.076), the duration of the first stage of labor (Begg's test P=1.000; Egger's test, P=0.282), and oxytocin augmen-

tation (Begg's test P=0.368; Egger's test P= 0.983) (**Figure 5**).

Discussion

In this meta-analysis, 8 studies (4 prospective and 4 retrospective studies) including 18832 parturients evaluated the effectiveness of REA and the risk of potential adverse effects when comparing to non-epidural methods of relieving pain in labour or no pian relief. The qualities of included studies were moderate.

Evidence from this meta-analysis indicated that parturients with REA had a lower rate of spontaneous vaginal delivery, an increased risk of instrumental delivery, and a longer duration in the second stage of labor when comparing to women who use non-epidural forms of analgesia or no analgesia at all. However, there was no statistically different in the rate of cesarean delivery, the rate of oxytocin augmentation, the duration of first stage of labor. We planned a subgroup analysis based on study design, and found that the study design did significantly influence and alter the rate of spontaneous vaginal delivery, the rate of instrumental delivery, and the duration of the second stage of labor.

Evidence from this review suggested that REA offered better pain relief in labor. However, measures of analgesia such as pain scores assessed using VAS, or numeric rating scales were not used at same standard scale between difference studies. So these data were inappropriate for synthesis. In this meta-analysis, although no quantitative synthesis was conducted, other maternal clinical outcomes (nausea, vomiting, and pruritus) and neonatal outcomes (Apgar scores and umbilical artery pH) stayed at an acceptable level and did not appear to differ between ropivacaine epidural and control groups as in other studies [27-30].

Trials varied in the characteristics of participants, labor management protocols and epidural regimen. These factors might influence the duration of labor, pain relief for oxytocin augmentation, maternal clinical outcomes (nausea, vomiting, and pruritus) and neonatal outcomes (Apgar scores and umbilical artery pH). Combining studies using a high concentration of a ropivacaine for epidural analgesia with low concentration techniques, and studies maintaining a block in the second stage of labor to those discontinuing might influenced some outcomes, in particular the duration of labor and instrumental delivery rates. Most women in the control group were randomized to opioids and, therefore, the effect on some outcomes might be applicable to the use of opioids in labor rather than all other non-epidural forms of analgesia or no pain relief. Some women randomized to non-epidural analgesia received epidural as well. To a lesser extent, some women in the epidural group did not receive the intervention due to rapid labor. We included only data based on an intention-to-treat analysis. So the evidence presented in this review needs to be interpreted taking these limitations into accout.

Sustantial heterogeneity was detected for all analyses except for the rate of instrumental delivery. No individual study was responsible for heterogeneity detected in the rate of spontaneous vaginal delivery, the rate of cesarean delivery, the rate of oxygocin augmentation and the duration of first stage of labor; we hypothesized that the heterogeneity was attributable to different ropivacaine doses used or different the design among included studies (prospective and retrospective). Heterogeneity was explored, and found that the trail by Huang [26] was responsible for the heterogeneity of the duration of second stage of labor

Except for the duration of the second stage of labor, neither Begg's funnel plot nor Egger's test demonstrated the presence of publication bias in spontaneous vaginal delivery, instrumental delivery, cesarean delivery, the duration of the first stage of labor, and oxytocin augmentation. The funnel plot of the second stage of labor was asymmetrical, which was attributed to the trail by Huang [26], due to that this article was retrospective study and had a large sample size.

Some limitations of our analysis should be noted. First, the number of eligible trials was relatively small, thus statistical power was low, and results were likely biased. Second, there was significant heterogeneity in the comparison of primary end points. Clinical application of our results should be cautious, since our meta-analysis was based on small-sized trials. Third, the studies reported women's perception of pain as an outcome but we could not extract

the data from these studies for meta-analytic analysis. These trials measured this outcome differently and reported the data in the formats that were not compatible with the software we used. Fourth, because of lacking data, it was not possible to make a meta-analysis to address the influence of ropivacaine epidural analgesia on maternal and neonatal outcomes. The last limitation of our meta-analysis was that not all included studies reported each outcome variable of interest in this meta-analysis.

Conclusions

In conclusion, REA affords more effective pain relief than NEA. However, women received REA had an increase in the duration of the second stage of labor and in the risk of instrumental delivery. The duration of the first stage of labor was longer in the REA group, but did not reach statistical significance. Whether an increase in the length of the second stage of labor constitutes prolongation necessitating instrumental delivery should be further studied. The decision about whether to have an REA should be made in consultation between the woman and her family members.

Despite a large number of trials are published, none of the included articles reported detailed data on adverse effects. Further well-designed clinical studies with large sample sizes are warranted to evaluate the efficacy and safety of REA in labor.

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Disclosure of conflict of interest

None.

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