



The Outcome Analysis of Epidural Analgesia on Labor in Primigravid Women: A Systematic Review and Meta-Analysis Focusing on Duration of Labor

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Abstract

Background: Epidural anesthesia is extensively used worldwide for pain relief in labor and more lately as an alternative and preferred form of anesthesia for caesarean sections; although its use is gaining universality, its outcome on the duration of labor is still debatable. Our meta-analysis aimed at analyzing the effects of epidural analgesia on duration of labor in primigravid women focusing on duration of labor.

Methods: We conducted a systematic literature search in PubMed and Embase (from the inception to July 2016). We calculated weighted mean differences (WMD) between the groups for continuous data, and corresponding 95% confidence intervals (CIs) using the random-effects model. We also performed a subgroup analysis for the effects of different types of studies on duration of labor. Statistical heterogeneity amongst the included studies was tested by I² indicator.

Results: Twelve studies, recruiting 16200 mothers overall, were selected for this systematic review and meta-analysis. The duration of first stage of labor was significantly prolonged in the epidural group by a mean of 2.66 (0.89, 4.43, p<0.00001) and significantly shortened the second stage of labor by a mean of -12.79 (-21.13, -4.45, p<0.00001). Moreover, the overall subgroup analyses shown significantly prolongation of the first stage of labor by the same mean of 2.66 (0.89, 4.43, p<0.00001).

Conclusion: The use of epidural analgesia for pain relief during labor is associated with prolongation of first stage of labor and does not prolong the second stage of labor.

Keywords: Epidural analgesia; Labor; Primigravid; Ropivacaine

Introduction

Epidural analgesia is not a new technique in obstetric practice. It was first documented in the 19th century into obstetric practice [1] but epidural analgesia for labor is a recent phenomenon. It is accepted that lumbar epidural analgesia is the most effective method of pain relief in labor, but its putative effects on labor and mode of delivery may influence clinical practice [2]. The method by which pain gets relief during labor includes regional, pudendal nerve blocks, epidural and systemic opioid analgesia. Intramuscular or intravenous opioids can provide an alternative in situations where regional analgesia is unavailable or contraindicated or if less invasive methods are preferred by the woman or obstetrician [3].

Epidural analgesia has gained universality due to its safety and administration of local amide anesthetic, in combination with opioids has become extensively used worldwide for pain relief in labor [4].

It has been documented that an epidural block prolongs the first stage of labor only slightly by about an hour on average and seems undoubtedly prolongs the second stage of labor [5]. Most previous studies have demonstrated that epidural analgesia was associated with a longer second stage of labor and a higher rate of operative vaginal delivery compared with labor without analgesia [6]. Although epidural analgesia is further gaining popularity, its outcome on the course of labor and method of delivery are still debatable [7], the adverse events of labor pain are various and affect both the mother and the fetus. Local anesthetics like bupivacaine, ropivacaine and lidocaine are frequently used. Despite being so popular, is not without complications, with hypotension, accidental dural puncture, infection,

intravascular placement high block, epidural hematoma [8], postdural puncture headache [9] and urinary retention. However, several studies have disputed whether epidural analgesia increases duration of labor, instrumental vaginal delivery, increase rate of cesarean section while other studies concluded that epidural analgesia does not adversely affect the progress of labor or increase the rate of cesarean section [10,11-18]. These issues remain debatable among practitioners today. Given the existing controversy, we performed a new systematic review and meta-analysis focusing on duration of labor by examining current evidences and provide a comprehensive analysis of the outcome of epidural analgesia given to primigravid women for pain relief during normal vaginal delivery.

Materials and Methods

Literature identification

We conducted a systematic search for randomized controlled trials

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(RCTs), prospective cohort studies and retrospective cohort studies referring to epidural analgesia during labor in PubMed, Embase and The Cochrane Library up to July 2016. The following terms: “epidural analgesia” or “labor” or “primigravid” and “ropivacaine” were searched in English language. In addition, no filter was applied in PubMed and Embase. We manually searched reference lists from identified articles and relevant reviews.

Inclusion and exclusion criteria

Studies involving the comparative evaluations of epidural analgesia group and no epidural group for labor analgesia were included in this systematic review and meta-analysis. The inclusion criteria were as follows: I) research group for primigravid singleton women; II) type of research for clinical studies, including randomized controlled trials, prospective cohort studies and retrospective cohort studies; III) intervention for the epidural analgesia; IV) request for pain relief. Exclusion criteria: I) All complicated pregnancies; II) BWT <60 kg and >120 kg; III) Age <20 years old; IV) incomplete data; V) reviews, commentaries, letters, case reports and conference abstracts and other within adequate data were exclude.

Quality evaluation and data extraction

Two authors (APA, WMR) independently extracted data and assessed the quality of the studies. For the disagreement or uncertainty, it was resolved by consensus or resort to Professor Bizhen Liao. We used the Cochrane handbook for systematic reviews of interventions for assessing the risk of bias for included studies [19]. There were three possible judgments: low risk of bias, high risk and if insufficient details were available, the judgment was reported that the risk of bias was unclear.

Statistical analysis

We carried our statistical analysis using the review manager software

(RevMan 5.3). We used random effect model for heterogeneous studies and calculated the weighted mean differences (WMD) with a two-tailed 95% confidence interval (CI) respectively. Statistic value I^2 to quantify the degree of inconsistency with a score of 25%, 50% and 75% representing low, moderate, and high levels of inconsistency. $P < 0.05$ was regarded as statistically significant.

Results

Studies selection

Twelve studies were selected for the meta-analysis by following the inclusion and exclusion criteria (Tables 1 and 2) [20-36]. A flow diagram of literature retrieval, screening, and study selection process is presented in Figure 1. Therefore, 7 RCTs, 3 Prospective observational studies and 2 retrospective studies were eventually included in present meta-analysis.

Baseline characteristics of included studies

The characteristics of the included studies are presented in Table 1. A total of 16200 parturient women were enrolled in the 7 RCTs (n=13791), 3 prospective cohort studies (n=1534) and 2 retrospective studies (n=875) and included in the review and meta-analysis. All included studies were small. The largest study recruited 12793 women with singleton. Age (MSD) of the participants ranged between 19.9 ± 3.6 years and 31.3 ± 5.2 years. Height and weight of the parturient women as MSD ranged between 160.1 cm ± 3.03 cm to 166 cm ± 7 cm and 64.65 kg ± 5 kg to 80 kg ± 14 kg, respectively. Among the important obstetric data as MSD, gestation period ranged between 37.76 ± 1.24 and 40 weeks and cervical diameter at the time of entry into the trial ranged between 0.99 ± 0.273 to 2.7 ± 1.2. To be noted, duration of labor was the only primary endpoint in all 12 studies.

Quality assessment

The quality of the 12 articles was assessed by the Cochrane

Study ID, Design, Year, Country	Arm	Sample	Demographics Age/Height/Weight	Obstetric characteristics Gestational Duration/Cervical dilation	Outcomes
Fettes et al. [30], RCT, 2006, UK	EA	40	27.1 ± 4.5/163.8 ± 6.2/74.1 ± 16.3	40.8 ± 1.3/2.7 ± 1.2	Duration of labor, mode of delivery & neonatal outcome
	No EA	40	25.8 ± 6.3/166.1 ± 7.6/76.2 ± 12.5	40.3 ± 1.3/2.7 ± 1.0	
Mousa et al. [23], RCT, 2010, Egypt	EA	60	26 ± 4.92/165.6 ± 3.59/75.07 ± 2.25	38.20 ± 1.18/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	60	25 ± 4.39/166.367 ± 2.16/77.13 ± 2.14	38.28 ± 0.94/-	
Mousa et al. [27], RCT, 2012, Egypt	EA	80	26.05 ± 3.04/161.6 ± 3.82/73.9 ± 4.01	38.01 ± 0.77/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	80	25.48 ± 4.07/160.1 ± 3.03/76.7 ± 3.09	37.99 ± 0.68/-	
Nafisi [2], RCT, 2006, Iran	EA	197	23.2 ± 2/154 ± 9/74 ± 12	38 ± 2/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	198	22.03 ± 3/155 ± 9/74 ± 13	39 ± 1/-	
Nakamura et al. [21], RCT 2009, Botucatu	EA	20	19.9 ± 3.6/BMI 28.3 ± 3.8/-	39.76 ± 8.3/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	20	21.4 ± 4.4/BMI 27.4 ± 3.1/-	39.47 ± 9.3/-	
Wang et al. [31], RCT, 2009, China	EA	6399	27.0 ± 4.4/161 ± 7/78 ± 16	40 (39-40)/-	Duration of labor, pain relief & mode of delivery
	No EA	6394	26.7 ± 4.8/161 ± 5/79 ± 14	40 (39-40)/-	
Wong et al. [32], RCT, 2005, China	EA	95	31.3 ± 5.2/165 ± 7/79 ± 14	40 (39-40)/1.23 ± 0.336	Duration of labor & mode of delivery
	No EA	108	31.3 ± 5.4/165 ± 7/80 ± 14	40 (39-40)/0.99 ± 0.273	
Agrawal et al. [24], Prospective, 2014, India	EA	60	28.13 ± 3.83/163.1 ± 8.31/65.06 ± 4.84	37.76 ± 1.24/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	60	26.95 ± 3.79/162.4 ± 8.33/64.65 ± 5.46	38.10 ± 1.24/-	
Liang et al. [33], Prospective, 2007, China	EA	264	28.9 ± 3.6/-/-	-	Duration of labor & mode of delivery
	No EA	319	28.1 ± 4.1/-/-	-	
Wu et al. [34], Retrospective, 2005, China	EA	190	26.5 ± 2.5/-/-	39.2 ± 1.1/-	Duration of labor, mode of delivery & neonatal outcome
	No EA	222	26.6 ± 2.7/-/-	39.0 ± 1.2/-	
Zhang et al. [35], Retrospective, 2005, China	EA	215	28.7 ± 2.6/-/-	39.0 ± 0.9/-	Duration of labor
	No EA	248	28.2 ± 2.4/-/-	39.0 ± 0.9/-	

EA=Epidural Analgesia; No EA=No Epidural Analgesia

Table 1: Important characteristics of the included studies.

handbook for systematic reviews of interventions for assessing the risk of bias for included studies [19]. There were three possible judgments: low risk of bias, high risk and if insufficient details were available, the judgment was reported that the risk of bias was unclear (Table 2). A low-level selection bias including publication bias was also evident from the visual examination of the funnel plot (Figures 2 and 3).

Effects of Epidural Analgesia on Duration of Labor

First stage of labor

Twelve studies included in this review and meta-analysis, a total of 11 studies reported the results for the duration of first stage of labor. Heterogeneity existed between studies ($I^2=95\%$, $P<0.003$). The random effects model was used to analyze the results of the duration of first stage of labor. Results show, epidural group involved 7923 women and no epidural group involved 8277 women and duration of first stage of labor rate was 95.72%; overall meta-analysis effect estimate difference=2.66 min; Mean (95%CI: 0.89, 4.43, $p<0.00001$, $Z=2.95$). Epidural group when compared to no epidural group, results indicates that duration of first stage of labor is prolonged in the group which did receive epidural analgesia by 2.66 min and reached statistical significance. A meta-

analysis of the effect of epidural analgesia on duration of first stage of labor in all studies (Figure 4).

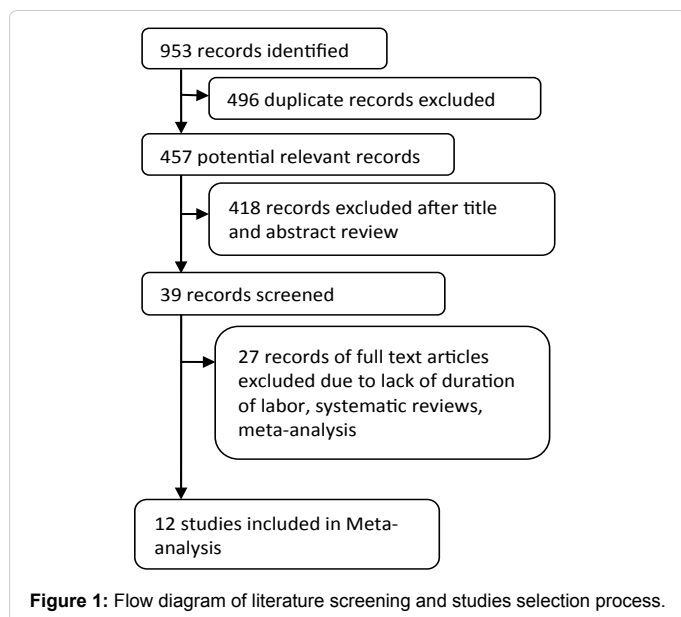
Second stage of labor

Twelve studies reported data on duration of second stage of labor. Heterogeneity existed between studies ($I^2=99\%$, $P<0.00001$). Using the random effects model, the results of duration of second stage of labor were analyzed. Results shown, epidural group involved 7848 women and no epidural group involved 8189 women and duration of second stage of labor at the rate of 95.84%; overall meta-analysis effect estimate difference=-12.79 min; Mean (95%CI: -21.13, -4.45, $p<0.00001$, $Z=3.01$). Epidural group when compared to no epidural group, results indicates that the duration of labor in the second stage was not prolonged in the epidural group by -12.79 min and reached statistical significance (Figure 5).

Subgroup analysis for the effects of studies types on duration of labor

We performed a subgroup analysis to determine the effects of different types of studies on duration of labor in the first and second stages. All 12 articles were included in the review, according to the study category studies were divided into 3 types: 1) randomized controlled trial; 2) prospective cohort studies and 3) retrospective studies. Out of 12 studies, only 11 studies reported on first stage of labor and second stage of labor. There existed different degrees of heterogeneity between the various types of studies, randomized controlled trials ($I^2=88\%$, $p<0.05$), prospective cohort studies ($I^2=97\%$, $P<0.05$), retrospective studies ($I^2=96\%$, $P<0.05$). Therefore, the random effects model analysis was used. In a randomized controlled trials 6871 cases of EA involving the object of study and involving 6880 cases of no EA and the duration rate was 99.87%, the effect estimate for meta-analysis mean difference=2.84 min (95%CI: -1.30, 6.99, $p<0.00001$, $Z=1.34$). The results suggest that use of epidural analgesia prolong the first stage of labor when compared to the group who did not take epidural analgesia by 2.84 min and reached statistical significance.

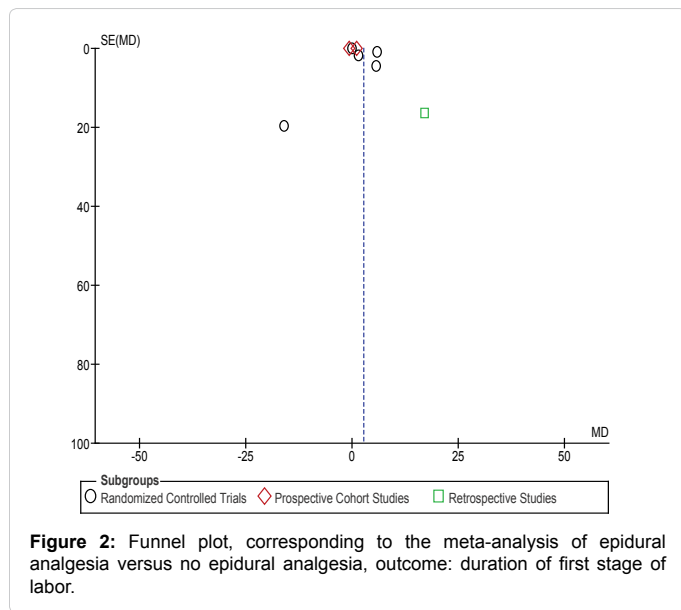
For the prospective cohort studies, EA study involved 647 cases and no EA involved 927 cases and the duration rate was 69.80%, the effect estimate for meta-analysis mean difference=1.06 min (95%CI: -1.54, 3.65, $p<0.00001$, $Z=0.80$). The results suggest that use of epidural analgesia prolong the first stage of labor when compared to the group who did not take epidural analgesia by 1.06 min and reached statistical significance. For the retrospective studies, EA study involved 405 cases and no EA involved 470 cases and the duration rate was 86.17%, the effect estimate for meta-analysis mean difference=67.68 min (95%CI:



Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Agrawal et al. [24], 2014	U	U	-	U	L	U	L
Fettes et al. [30], 2006	L	L	L	U	U	U	U
Liang et al. [33], 2007	L	L	U	U	L	U	L
Mousa et al. [23], 2010	L	L	U	U	U	U	U
Mousa et al. [27], 2012	L	L	L	L	L	U	L
Nafisi [2], 2006	U	U	U	U	L	U	L
Nakamura et al. [21], 2009	L	L	U	U	U	U	L
Sienko et al. [36], 2005	U	U	U	U	U	U	U
Wang et al. [31], 2009	L	L	L	U	U	U	L
Wong et al. [32], 2005	L	L	U	U	U	U	U
Wu et al. [34], 2005	U	U	U	U	U	U	L
Zhang et al. [35], 2005	U	U	U	U	U	U	L

H=high risk; L=low risk; U=Unclear risk

Table 2: Risk of bias assessment in the included studies.

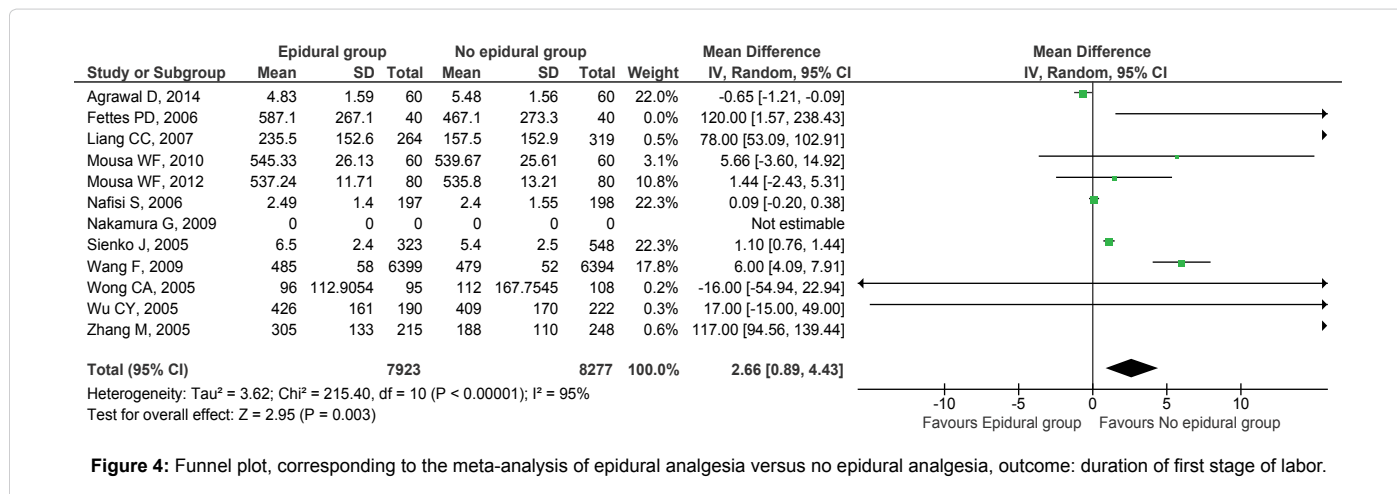
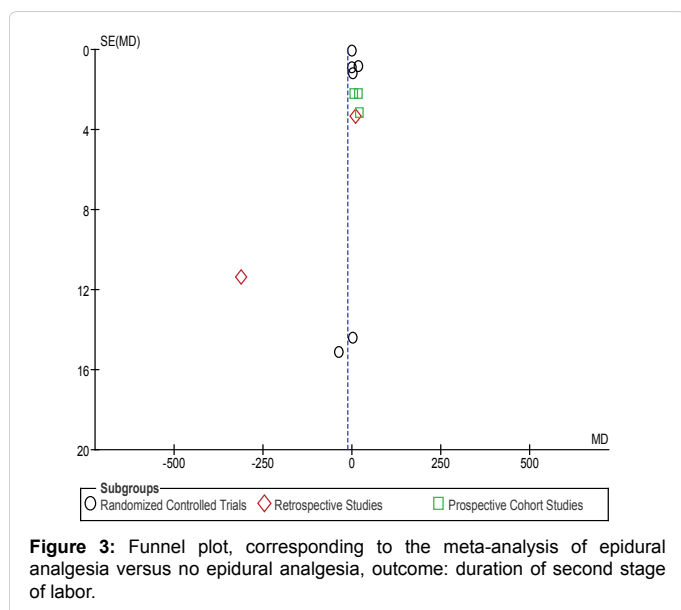


-30.31, 165.67, $p < 0.00001$, $Z = 1.35$). The results suggest that use of epidural analgesia prolong the first stage of labor when compared to the group who did not take epidural analgesia by 67.68 min and reached statistical significance. The details of effects of studies types on duration of first stage of labor are mentioned in Figure 6.

Another sub group analyzes the effects of different types of studies on duration of labor in the second stage. There existed different degrees of heterogeneity between the various types of studies, randomized controlled trials ($I^2 = 99\%$, $p < 0.05$), prospective cohort studies ($I^2 = 100\%$, $p < 0.05$), retrospective studies ($I^2 = 91\%$, $p < 0.05$). Therefore, the random effects model analysis was used. In a randomized controlled trials 6796 cases of EA involving the object of study and involving 6792 cases of no EA and the duration rate for second stage of labor was 100%, the effect estimate for meta-analysis mean difference = 2.52 min (95%CI: -4.94, 9.97, $p < 0.00001$, $Z = 0.66$). The results show no much difference between two groups. For retrospective studies, EA study involved 405 cases and no EA involved 470 cases and the duration rate was 86.17%, the effect estimate for meta-analysis mean difference = -149.84 (95%CI: -463.41, 163.78), $p < 0.00001$, $Z = 0.94$). The results suggest that the use of epidural analgesia does not prolong the second stage of labor when compared to the group who did not receive epidural analgesia. For the prospective cohort studies, EA study involved 647 cases and no EA involved 927 and the duration of 69.80%, the effect estimate for meta-analysis mean difference = 14.76 (95%CI: 5.28, 24.24, $p < 0.00001$, $Z = 3.05$). The results show no much difference between two groups. The details of effects of studies types on duration of second stage of labor are mentioned in Figure 7.

Discussion

The present study revealed that the use of epidural analgesia in primigravid women prolong the first stage of labor and does not prolong the second stage of labor. All 12 included studies looked at the duration of labor endpoint notably, the first and second stage. In the studies, effect of epidural and combined spinal epidural technique using bupivacaine 0.08% and fentanyl 2 µg/ml shown no much significance for duration of labor between the two groups (SMD: 0.30, 95%CI: -0.47 to 1.07, $p = 0.45$, $Z = 0.76$) [20,21]. Study compared continuous epidural analgesia (CEA) versus patient-controlled epidural analgesia (PCEA) also reported no statistical significance on duration of labor [22]. Another study compared 0.5% lidocaine with fentanyl versus 0.08% ropivacaine with fentanyl and demonstrated no significant differences in duration of labor (SMD: -0.25, 95%CI: -0.61 to 0.11) [23]. These



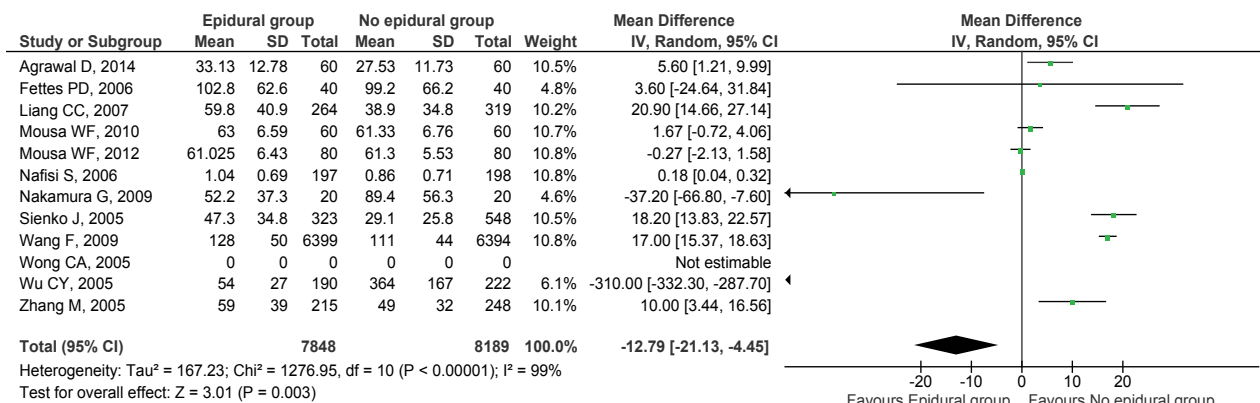


Figure 5: Forest plot for comparison of epidural group and control group and outcome shown as duration of second stage of labor.

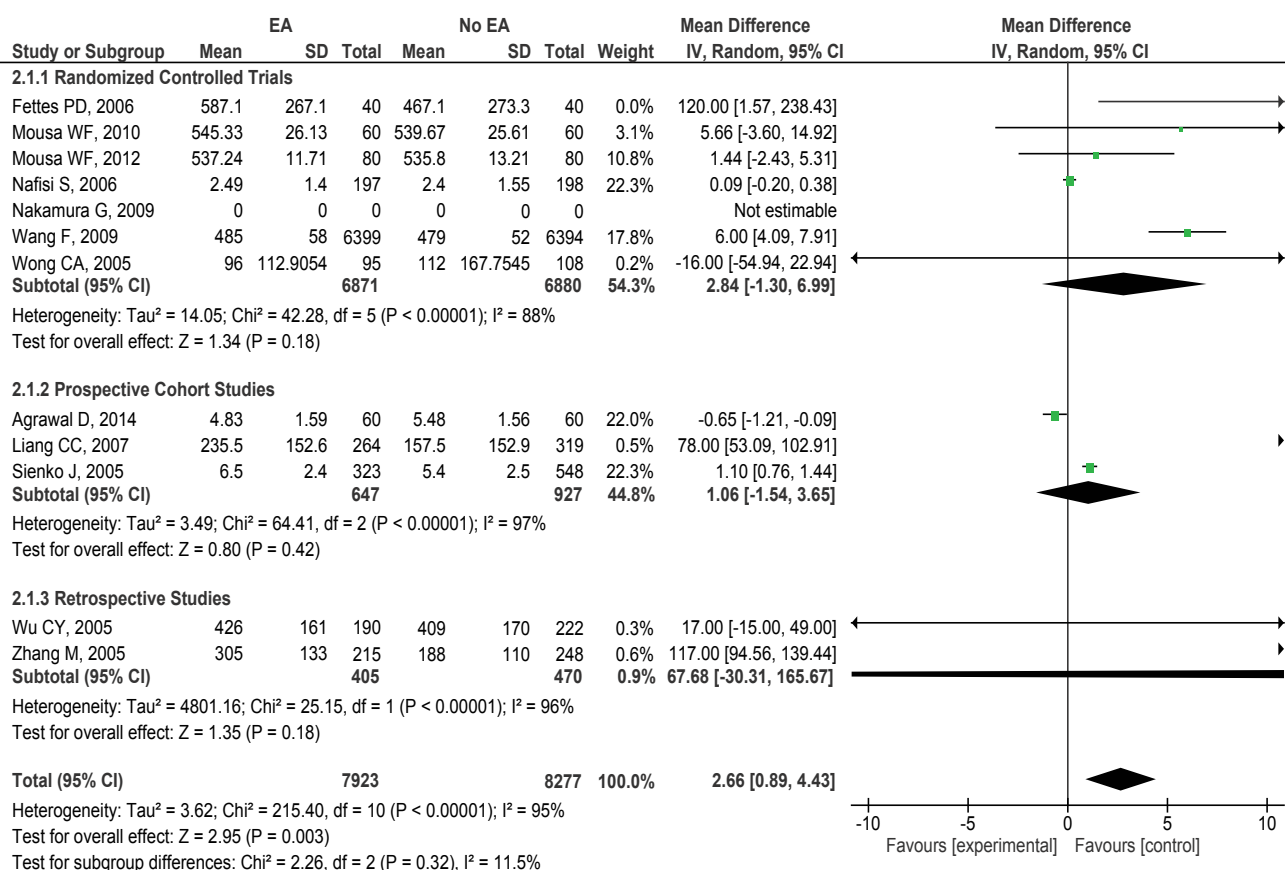


Figure 6: Forest plot on the influence of the studies type on duration of first stage of labor.

findings did not differ with the findings in a randomized, prospective, controlled trial which found that the use of epidural analgesia with 1% lidocaine does not prolong the active-first and second stages of labor [2]. Also, Agrawal et al. [24] found that epidural analgesia by ropivacaine in Indian nulliparous resulted in shorter duration of first stage and prolongs duration of second stage of labor compared with parturients without analgesia. The study comparing 0.1% bupivacaine plus 0.5% tramadol versus nalbuphine 10 mg I/M without epidural analgesia reported that total duration of labor shown that group A had longer

time 7.57 h ± 1.13 h compared to group B 4.77 h ± 1.21 h (SMD: -2.37, 95%CI: -2.89 to -1.86) [25]. Margaret et al. [26] compared bupivacaine and fentanyl versus fentanyl only reported no significance difference in the median duration of second stage of labor between the two groups (SMD: 0.01, 95%CI: -0.21 to 0.24). On the other hand, Mousa et al. [27] compared epidural analgesia versus no analgesia reported no significant differences in the duration of labor between the two groups.

Epidural analgesia has been shown to reduce the active phase of

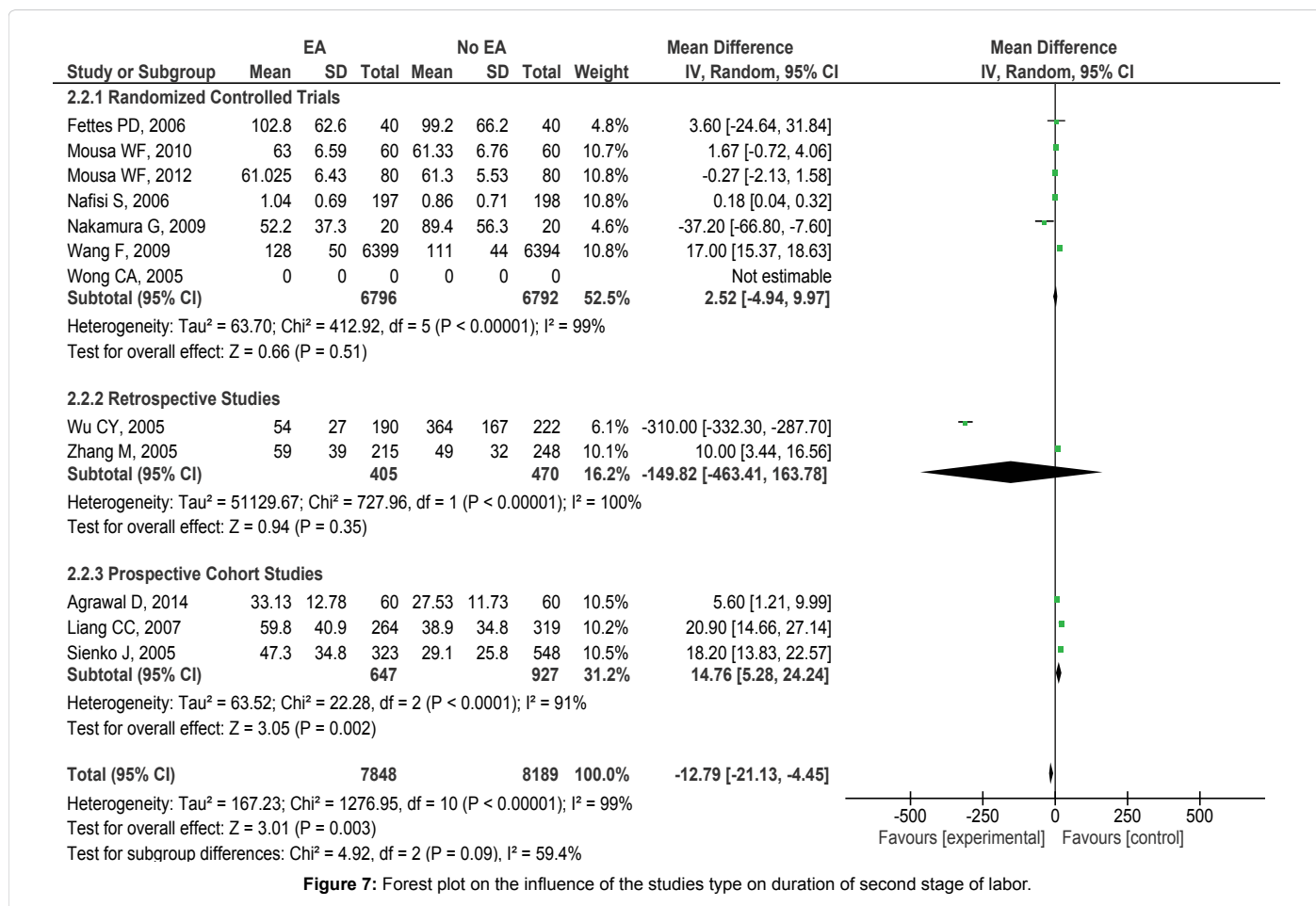


Figure 7: Forest plot on the influence of the studies type on duration of second stage of labor.

first stage of labor [28] as well as increasing the risk of prolonged first and second stage of labor [29-36]. Interestingly, the present study found that use of epidural analgesia can prolong the duration of first stage of labor in primigravid women by 2.66 min and does not prolong the second stage of labor SMD 2.66, (95%CI: 0.89, 4.43, p<0.00001, Z=2.95). Also, our subgroup analyses of study types shown that for randomized controlled trials, the results shown that use of epidural analgesia prolong the first stage of labor when compared to the group who did not take epidural analgesia by 2.84 min and reached statistical significance whereas does not prolong second stage of labor. For prospective studies use of epidural analgesia prolongs duration of first stage of labor by 1.06 min whereas shows no much differences in the second stage of labor. For retrospective studies use of epidural analgesia prolong duration of first stage of labor by 67.68 min whereas does not prolong the second stage of labor. Therefore, it appears that epidural analgesia when used for pain relief during labor is associated with prolongation of first stage of labor and does not prolong the second stage of labor. However, caution is warranted when interpreting the results given that all studies included in the review had used different analgesic drugs with different concentrations and had different number of patients.

The main limitation of our study is that some of the studies were non-randomized controlled study. According to the inclusion and exclusion criteria, we screened 39 clinical studies of epidural analgesia in labor, after careful verification, 27 articles were excluded and finally 12 articles were included, 7 RCTs, 3 prospective studies and 2 retrospective studies. Therefore, the choice of technique was left to the individual

anesthesiologist, even though maternal demographic characteristics and cervical dilation at the time of analgesia were similar in both groups. We studied parturient who were nulliparous. Our results may not apply to other parturient or other epidural analgesia labor protocols. We found that epidural analgesia prolonged the duration of first stage of labor in the groups which requested analgesia for pain relief during vaginal delivery and did not prolong the second stage of labor.

Conclusion

The use of epidural analgesia for pain relief during labor is associated with prolongation of first stage of labor and does not prolong the second stage of labor.

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