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SYSTEMATIC REVIEW

Comparison of dexmedetomidine and lipophilic opioids as adjuvants to local anesthetics for epidural labor analgesia: a meta-analysis of randomized controlled trials

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Abstract

The aim of this study is to evaluate the benefits of dexmedetomidine in epidural labor analgesia compared with lipophilic opioids. The databases of PubMed, Embase, Cochrane Library, Web of Science, Wanfang, and SinoMed were searched from inception to Mar. 25, 2021 for randomized controlled trials (RCT) that assessed dexmedetomidine versus lipophilic opioids as adjuvants to local anesthetics in epidural labor analgesia. Meta-analyses were conducted with RevMan 5.3, and a random-effects model was adopted. A total of 11 RCTs involving 1099 parturients were enrolled. The results showed that, compared with the control group, dexmedetomidine significantly reduced Visual Analogue Scale (VAS) scores both at 30 minutes after induction [weighted mean difference (WMD) = –0.40, 95% CI: –0.61 to –0.20] and on delivery (WMD = –0.83, 95% CI: –1.15 to –0.50), reduced analgesic consumption (WMD = –6.29 mL, 95% CI: –10.49 to –2.10), shortened the duration of the first (WMD = –9.58 minutes, 95% CI: –18.12 to –1.04) and second (WMD = –1.66 minutes, 95% CI: –3.20 to –0.12) stage of labor, increased maternal bradycardia [risk ratio (RR) = 2.44, 95% CI: 1.31 to 4.53] and motor blockade (RR = 5.30, 95% CI: 2.21 to 12.73), reduced nausea/vomiting (RR = 0.34, 95% CI: 0.20 to 0.57), pruritis (RR= 0.19, 95% CI: 0.06 to 0.58) and shivering (RR = 0.37, 95% CI: 0.18 to 0.77). There was no significant difference between groups in the rate of instrumental delivery ($p = 0.68$), and cesarean delivery ($p = 0.40$), Apgar scores at 1 minute ($p = 0.24$), at 5 minutes ($p = 0.36$), and the umbilical arterial PH ($p = 0.16$). In summary, compared to lipophilic opioids, dexmedetomidine for epidural labor analgesia reduced analgesic agent consumption and resulted in fewer maternal complications.

Keywords

Dexmedetomidine; Lipophilic opioids; Adjuvant; Epidural labor analgesia; Meta-analysis

1. Introduction

Effective relief of labor pain can improve maternal satisfaction and plays an important role in reducing the rate of cesarean delivery, and ensuring maternal and fetal safety [1]. Various methods have been widely used to relieve labor pain. An epidural block remains the most common method of providing pain relief during labor [2, 3]. Lipophilic opioids (such as fentanyl and sufentanil) are the most common adjuvants to local anesthetic solutions to reduce the concentration of local anesthetics, prolong analgesia duration and improve the overall quality of analgesia [4]. However, the addition of opioids increases the incidence of maternal pruritis, urinary retention, nausea and vomiting [5–7].

Given the side effects of opioids, the α-2 adrenergic agonists (clonidine and dexmedetomidine) are reasonable options as adjuvants to local anesthetics to improve epidural analgesia. Clonidine is considered a useful adjuvant in labor analgesia, but dexmedetomidine is considered to be a better adjuvant than clonidine in epidural anesthesia [8–10] as dexmedetomidine is a highly selective α-2 adrenergic agonist with an affinity eight times greater than clonidine [11]. Dexmedetomidine inhibits pain transmission by binding to pre- and post-synaptic α-2 receptors in the substantia gelatinosa of the dorsal horn of the spinal cord [12]. It can prolong the duration of analgesia when combined with local anesthetics [8], has high placental retention (0.77 maternal/fetal index) and also promotes the progress of labor as it increases the frequency and amplitude

of uterine contractions in a dose-dependent fashion [13, 14]. It provides beneficial effects when administered through an epidural route including sedation, anti-anxiety, and analgesia without respiratory depression. However, it can cause bradycardia and hypotension, especially at higher doses [15, 16].

The use of dexmedetomidine for epidural labor analgesia has increased in recent years [9, 17, 18]. A previous meta-analysis found that the addition of dexmedetomidine to other anesthetic agents during epidural procedures provided a longer duration of analgesia and higher sedation scores with insignificant side effects [19]. However, no meta-analysis has systematically evaluated the efficacy of dexmedetomidine versus lipophilic opioids in epidural labor analgesia. Therefore, we performed this meta-analysis to compare the benefits of dexmedetomidine versus lipophilic opiods in parturients receiving epidural analgesia during delivery.

2. Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20] and registered on PROSPERO (register number CRD42020211533).

2.1 Search strategy

We searched databases including PubMed, Embase, Cochrane Library, Web of Science, Wanfang, and SinoMed from inception to Mar. 25, 2021 using the flowing keywords: "Dexmedetomidine OR DEX" AND "Lipophilic opioids OR Fentanyl OR Sufentanil" AND "Epidural" AND "Labor analgesia OR Vaginal delivery". There were no language limitations. Furthermore, the references of eligible articles were identified to prevent missing articles.

2.2 Inclusion and exclusion criteria

We included studies that met the following inclusion criteria: (1) they are randomized controlled trials (RCTs); (2) the studies included full-term healthy parturients scheduled for vaginal delivery; (3) studies compared dexmedetomidine and lipophilic opioids as adjuvants to the same background of local anesthetic in epidural labor analgesia. The exclusion criteria were as follows: (1) the data was not available in the abstract or full text; (2) the data could not be extracted; (3) the study was a case report, letter, editorial, or review.

2.3 Primary and secondary outcomes

The primary outcomes were the analgesic effect (pain scores at 30 minutes after induction and on delivery), total analgesic consumption, and duration of labor. The secondary outcomes were maternal complications (including hypotension, bradycardia, nausea and vomiting, pruritis, shivering, motor blockade), mode of delivery (instrumental and cesarean delivery rate), and neonatal outcomes (Apgar scores at 1 and 5 minutes, umbilical arterial PH).

2.4 Data extraction and quality assessment

Data extraction and quality assessment were performed independently by 2 authors (ML and JC). Discrepancies were resolved through discussion with another author (DM). Data extraction was performed using electronic forms. General characteristics of included studies (first author, publication year, and country), number of participants, the regimens of local anesthetics and adjuvants, and outcomes were extracted. Data reported as graphs were extracted by GetData Graph Digitizer software (version 2.26, Canopus, Japan).

The quality of each included study was assessed with the Cochrane Collaboration Risk of Bias Assessment Tool for the assessment of RCTs [21] across all domains: random sequence generation, allocation concealment, blinding, outcome assessment, incomplete outcome data, selective reporting, and other bias, and each of them was graded as high, unclear or low risk of bias.

2.5 Statistical analysis

Meta-analyses were conducted with Review Manager (version 5.3, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Weighted mean difference (WMD) with 95% confidence intervals (CIs) was described for continuous variables, and risk ratio (RR) with 95% CIs for dichotomous variables. We used a random effect model (REM) as we assumed the heterogeneity to be substantial. Funnel plots were not conducted to detect publication bias owing to the limited number of studies included. The heterogeneity was quantified by coefficient I^2, and I^2 >50% indicated substantial heterogeneity. Sensitivity analysis was conducted by removing each study one by one to explore the heterogeneity when substantial heterogeneity exists. $p < 0.05$ was considered statistically significant.

We conducted a trial sequential analysis (TSA) on the co-primary outcomes to assess the risk of random errors [22]. Analysis was conducted using TSA software (version 0.9.5.10 beta, Copenhagen Trial Unit, Denmark, available from http://www.ctu.dk/tsa/). An α error of 5%, a β error of 0.20, and two-sided testing were used for this analysis. We calculated the required sample size based on the calculated WMD and variance estimated from the respective meta-analysis. The O'Brien-Fleming α-spending function was used to create boundaries for concluding superiority, inferiority, or futility.

3. Results

3.1 Selected studies

263 studies were initially identified, and 2 additional studies were identified through other sources. After duplicates were removed, 149 studies remained for abstract screening, and 17 studies were obtained for full-text reading. Finally, 11 RCTs [9, 17, 23–31] were included in the meta-analysis after the full-text review (Fig. 1).

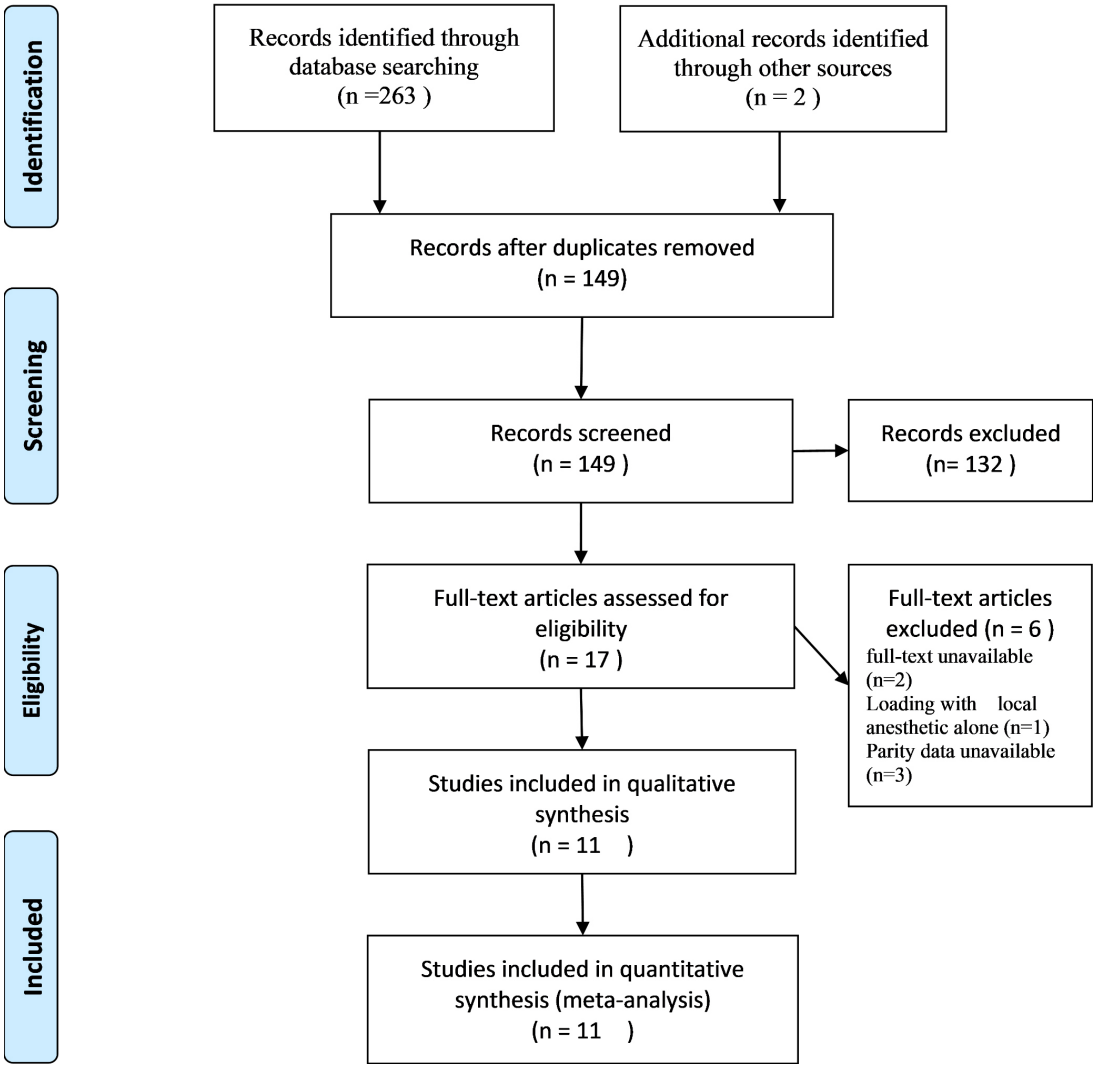

FIGURE 1. Flow diagram of study selection (PRISMA).

3.2 Study characteristics and quality assessment

A total of 1099 healthy adult parturients scheduled for epidural analgesia during labor were involved in the meta-analysis, 551 cases were assigned to the dexmedetomidine group, and 548 cases to the control group. Local anesthetics used included bupivacaine [9, 17, 25], ropivacaine [23, 24, 27–31] and levobupivacaine [26]. Adjuvants used in the control group included fentanyl [9, 17, 25, 31] and sufentanil [23, 24, 26–30]. There were four groups and two backgrounds of local anesthetics in the study by Cheng *et al.* [24], thus, the total number of comparisons obtained was 12. The characteristics of the included trials are shown in Table 1 (Ref. [9, 17, 23–31]), and the Cochrane risk bias assessment results are displayed in Fig. 2.

3.3 Primary outcomes

Pain was evaluated using Visual Analogue Scale (VAS) scores in most studies except one [25]. Compared with lipophilic opioids, dexmedetomidine reduced VAS scores both at 30 minutes after induction (WMD = –0.40, 95% CI: –0.61 to –0.20, $p = 0.0001$, $I^2 = 61\%$) and on delivery (WMD = –0.83, 95% CI: –1.15 to –0.50, $p < 0.00001$, $I^2 = 92\%$) (Fig. 3), both with significant heterogeneity (61%, 92% respectively). In the sensitivity analysis, the VAS scores at 30 minutes after induction was sensitive in one study [17], but the pooled WMD remained statistically significant after exclusion of this study (WMD = –0.31, 95% CI: –0.46 to –0.15, $p = 0.0002$, $I^2 = 31\%$); while the VAS scores on delivery was not sensitive to a single study, and the pooled WMD remained statistically significant after exclusion of individual studies. All the trial sequential monitoring boundaries were crossed by cumulative Z-curve in TSA. This indicates that dexmedetomidine decreasing VAS scores both at 30 minutes after induction and on delivery compared with lipophilic opioids were without the risk of random errors (Figs. 4,5). Therefore, a conclusion had likely been reached.

Three studies [23, 30, 31] reported the total analgesic consumption, and the meta-analysis indicated lesser analgesic consumption (WMD = –6.29 mL, 95% CI: –10.49 to –2.10, $p = 0.003$, $I^2 = 0\%$) in the dexmedetomidine group (Fig. 6). All the trial sequential monitoring boundaries were crossed by the cumulative Z-curve, indicating that dexmedetomidine reduced analgesic consumption compared with lipophilic opioids without the risk of random errors (Fig. 7).

TABLE 1. Characteristics of included RCTs.

Study	Participants	Intervention (sample size)	Control (sample size)	Anesthetic administration	Outcomes
Selim MF 2012 [9] Egypt	Primiparas and multiparas	0.25% Bupivacaine 12 mL + DEX 1 μg/kg = 17 mL (44)	0.25% Bupivacaine 12 mL + Fentanyl 1 μg/kg = 17 mL (43)	Bolus injection + rescue	1, 3, 4, 5, 7.
Karuna H 2016 [17] Bangalore	Primiparas	0.0625% Bupivacaine + DEX 1.5 μg/mL = 15 mL (30)	0.0625% Bupivacaine + 2 μg/mL Fentanyl = 15 mL (30)	Bolus injection + rescue	1, 3, 4, 5.
Zhang T 2019 [23] China	Primiparas	0.1% Ropivacaine + DEX 0.5 µg/mL (36)	0.1% Ropivacaine + Sufentanil 0.5 µg/mL (34)	CEI + PCEA	1, 2, 3, 4, 5, 6.
Cheng Q 2019 [24] China	Primiparas	0.125% Ropivacaine + DEX 0.5 µg/mL (40)	0.125% Ropivacaine + Sufentanil 0.5 µg/mL (40)	CEI + PCEA	1, 2, 3, 4, 5, 6.
Cheng Q 2019 [24] China	Primiparas	0.08% Ropivacaine + DEX 0.5 µg/mL (40)	0.08% Ropivacaine + Sufentanil 0.5 µg/mL (40)	CEI + PCEA	1, 2, 3, 4, 5, 6.
Soliman R 2016 [25] Saudi Arabia	Primiparas and multiparas	0.25% Bupivacaine 13 mL + DEX 1 μg/kg = 15 mL (85)	0.25% Bupivacaine 13 mL + Fentanyl 1 μg/kg = 15 mL (85)	Bolus injection + rescue	3, 4, 5, 6.
Huang Y 2016 [26] China	Primiparas	0.1% Levobupivacaine + DEX 0.5 µg/mL (60)	0.1% Levobupivacaine + Sufentanil 0.5 µg/mL (60)	CEI + PCEA	1, 2, 3, 4, 5.
Zhu X 2018 [27] China	Primiparas	0.1% Ropivacaine + DEX 2 µg/mL (56)	0.1% Ropivacaine + Sufentanil 0.5 µg/mL (56)	CEI + PCEA	1, 2, 5, 6.
Mao S 2017 [28] China	Primiparas	0.1% Ropivacaine + DEX 0.5 µg/mL (40)	0.1% Ropivacaine + Sufentanil 0.5 µg/mL (40)	CEI + PCEA	1, 2, 3, 4, 5, 6.
Shen S 2020 [29] China	Primiparas	0.1% Ropivacaine + DEX 1 µg/mL (60)	0.1% Ropivacaine + Fentanyl 2 µg/mL (60)	PIEB + PCEA	1, 2, 3, 4, 5.
Tang Y 2019 [30] China	Primiparas	0.09% Ropivacaine + DEX 0.5 µg/mL (33)	0.09% Ropivacaine + Sufentanil 0.5 µg/mL (30)	PIEB + PCEA	1, 2, 3, 4, 5, 7.
Yu C 2020 [31] China	Primiparas	0.1% Ropivacaine + DEX 0.5 µg/mL (30)	0.1% Ropivacaine + Fentanyl 2 µg/mL (30)	PIEB + PCEA	1, 2, 4, 5, 7.

DEX, dexmedetomidine; CEI, continuous epidural infusion; PCEA, patient-controlled epidural analgesia; PIEB, programmed intermittent epidural bolus.
1: visual analogue scale (VAS) scores, 2: duration of labor, 3: mode of delivery, 4: maternal complications, 5: neonatal Apgar scores, 6: umbilical cord blood gas, 7: total analgesic consumption.

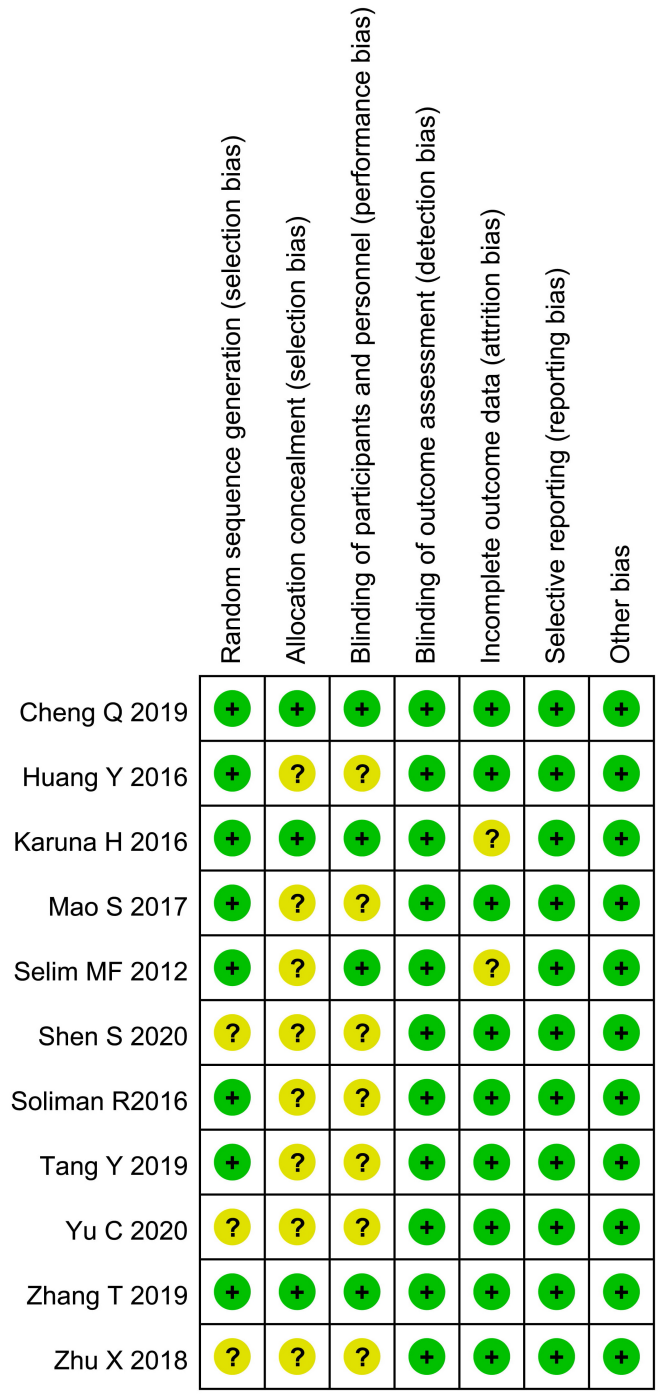

FIGURE 2. Risk of bias summary. Yellow, unclear risk of bias; red, high risk of bias; green, low risk of bias.

Eight studies [23, 24, 26–31] involving only primiparas reported the duration of labor. The meta-analysis indicated that the duration of the first stage (WMD = –9.58 minutes, 95% CI: –18.12 to –1.04, $p = 0.03$, $I^2 = 1\%$) and the second stage of labor (WMD = –1.66 minutes, 95% CI: –3.20 to –0.12, $p = 0.03$, $I^2 = 0\%$) were both shorter in the dexmedetomidine group (Fig. 8). However, the cumulative Z-curve of both neither crossed the trial sequential monitoring boundary nor the required information size (Figs. 9,10), the futility boundaries were not crossed by Z-curves before the information size was achieved, indicating that the possibility of type 1 errors cannot be excluded.

3.4 Secondary outcomes

The definition of hypotension varied among studies: mean arterial blood (MAP) decrease >20% from baseline [9, 17, 24, 25], systolic blood pressure (SBP) <90 mmHg [17, 28, 30, 31] or decrease >20% from baseline [23], MAP <70 mmHg [29]. Maternal bradycardia also varied with definitions: heart rate <60 bpm [9, 17, 24, 25, 31], <50 bpm [29, 30] or decrease >20% from baseline [23]. The data of nausea and vomiting was collected independently in three studies [9, 24, 28] and presented as a parameter in six studies [17, 23, 25, 29–31]. We integrated the data as nausea and vomiting, but the scoring criteria for nausea and vomiting were not described in detail in any of the included studies. Motor blockade was defined as Bromage scores ≥1.

The Meta-analysis resulted in no statistically significant difference between groups in the incidence of hypotension (RR = 1.12, 95% CI: 0.48 to 2.65, $p = 0.79$, $I^2 = 45\%$), but more bradycardia (RR = 2.44, 95% CI: 1.31 to 4.53, $p = 0.005$, $I^2 = 0\%$) and motor blockade (RR = 5.30, 95% CI: 2.21 to 12.73, $p = 0.0002$, $I^2 = 0\%$), less nausea and vomiting (RR = 0.34, 95% CI: 0.20 to 0.57, $p < 0.0001$, $I^2 = 0\%$), pruritis (RR = 0.19, 95% CI: 0.06 to 0.58, $p = 0.004$, $I^2 = 0\%$), and shivering (RR = 0.37, 95% CI: 0.18 to 0.77, $p = 0.008$, $I^2 = 0\%$) were found in the dexmedetomidine group (Table 2).

The meta-analysis also resulted in no statistically significant difference between groups in instrumental delivery rate ($p = 0.68$), cesarean delivery rate ($p = 0.40$), the Apgar scores at 1 minute ($p = 0.24$), at 5 minutes ($p = 0.36$), and the umbilical arterial PH ($p = 0.16$) (Table 2).

4. Discussion

Our meta-analysis provides evidence of the possible advantage of dexmedetomidine over lipophilic opioids as adjuvants to local anesthetics in epidural labor analgesia. A total of 1099 parturients from 11 studies were included. The included parturients in both groups were comparable in terms of baseline demographics. Epidural dexmedetomidine was found to result in lower VAS scores at 30 minutes after induction and on delivery (–0.40/–0.83). Although the differences in VAS scores were statistically significant, they may have little clinical importance. Nevertheless, epidural dexmedetomidine did reduce total analgesic consumption, and seemed to have a positive effect on shortening both the first and second stage of labor (WMD = –9.58, –1.66 minutes, respectively). However, with an inadequate sample size, no firm conclusions about shortening the duration of labor before the word can be drawn based on the present evidence. Dexmedetomidine reduced maternal adverse effects including nausea and vomiting, pruritis, and shivering, but increased bradycardia and motor blockade. It had no impact on the mode of delivery and neonatal outcomes.

With regards to analgesic effect, we chose to examine VAS scores at 30 minutes after induction and on delivery, since the onset of analgesia was all within 30 minutes. There was a statistically significant reduction in VAS scores in the dexmedetomidine group, but both by less than 1 point at the two time points. Although epidural dexmedetomidine did not improve the analgesic effect, as the minimum clinically

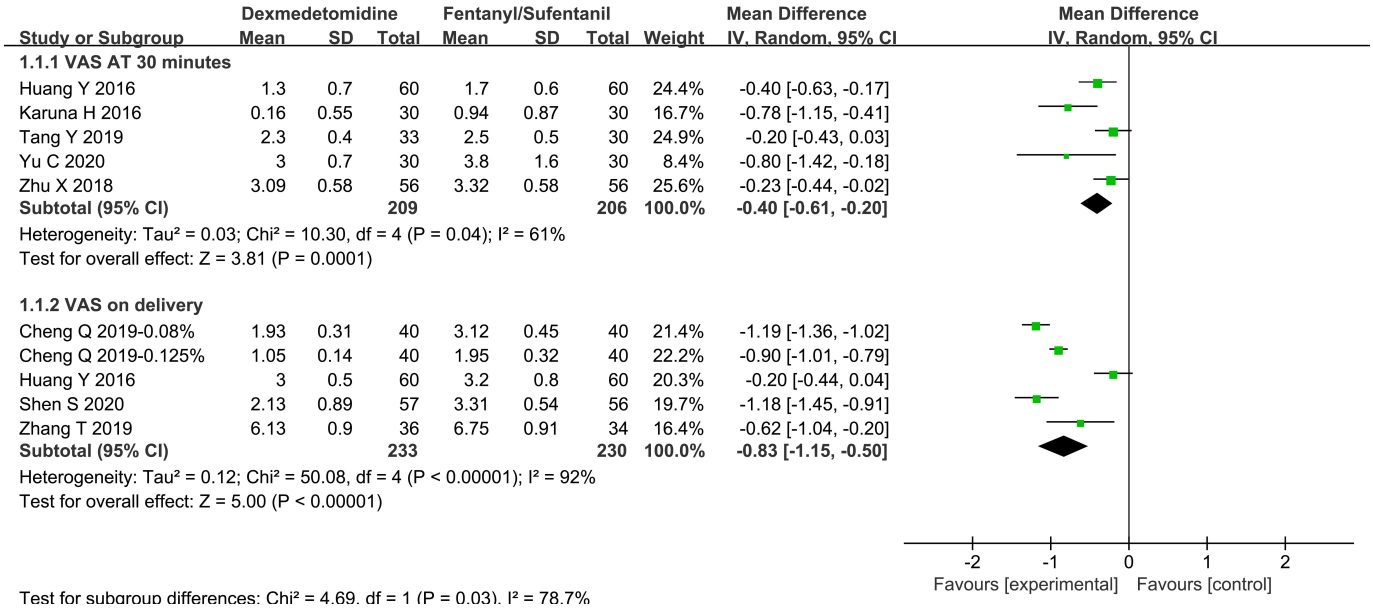

FIGURE 3. Forest plots for the meta-analysis of VAS at 30 minutes after induction and on delivery.

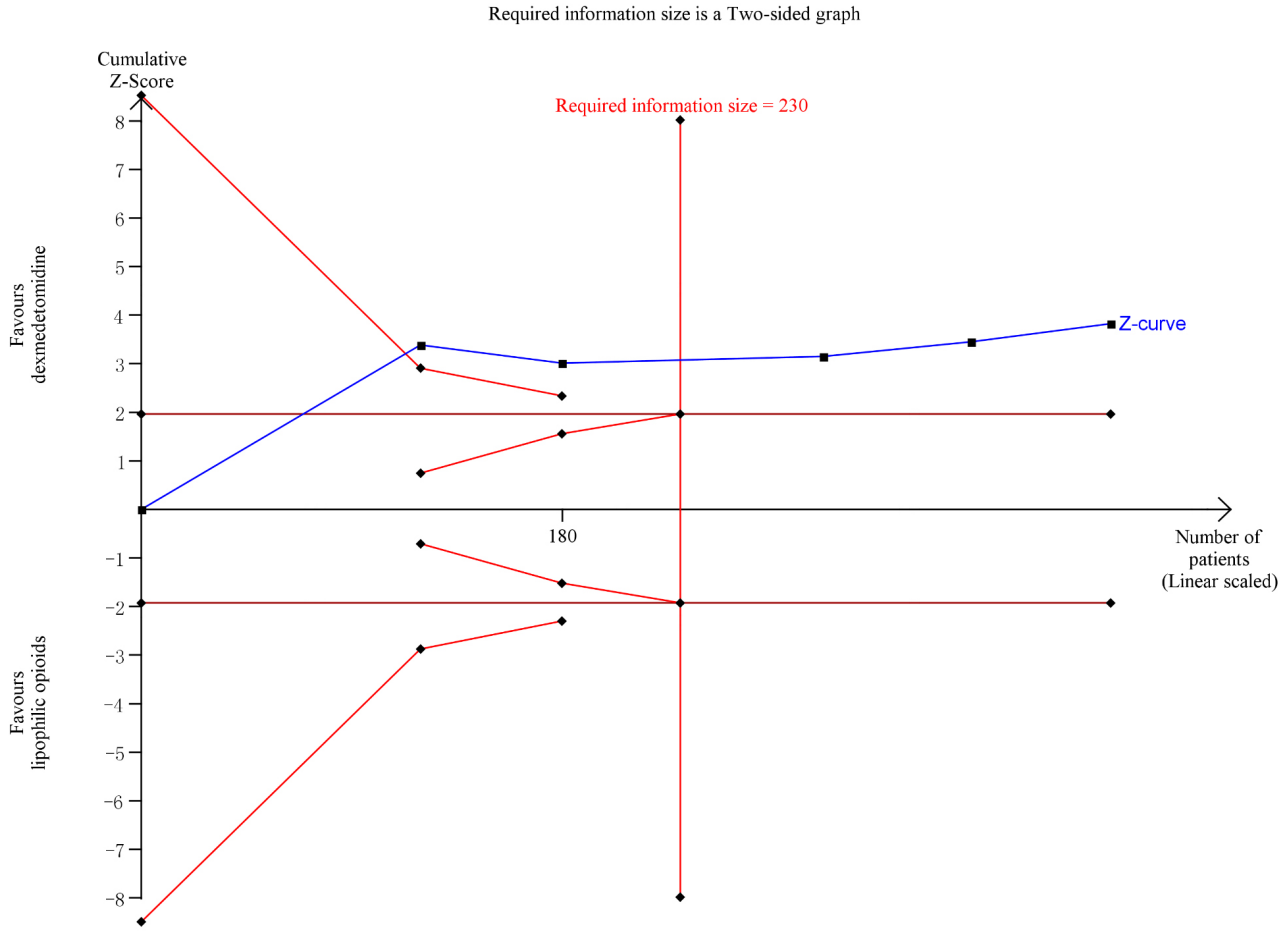

FIGURE 4. Trial sequential analysis for VAS scores both at 30 minutes after induction.

important difference in VAS scores for parturients was approximately 18 mm [32], it did reduce total analgesic consumption.

Epidural dexmedetomidine probably shortened the duration of labor compared to lipophilic opioids. This may be related to its direct increase in uterine contractions [14] or reduced total analgesic consumption. However, different local anesthetics with different doses and concentrations, and different modes of epidural maintenance may have confounded the effect of dexmedetomidine, as noted by the TSA results. In view of the previous studies showing that epidural analgesia prolongs

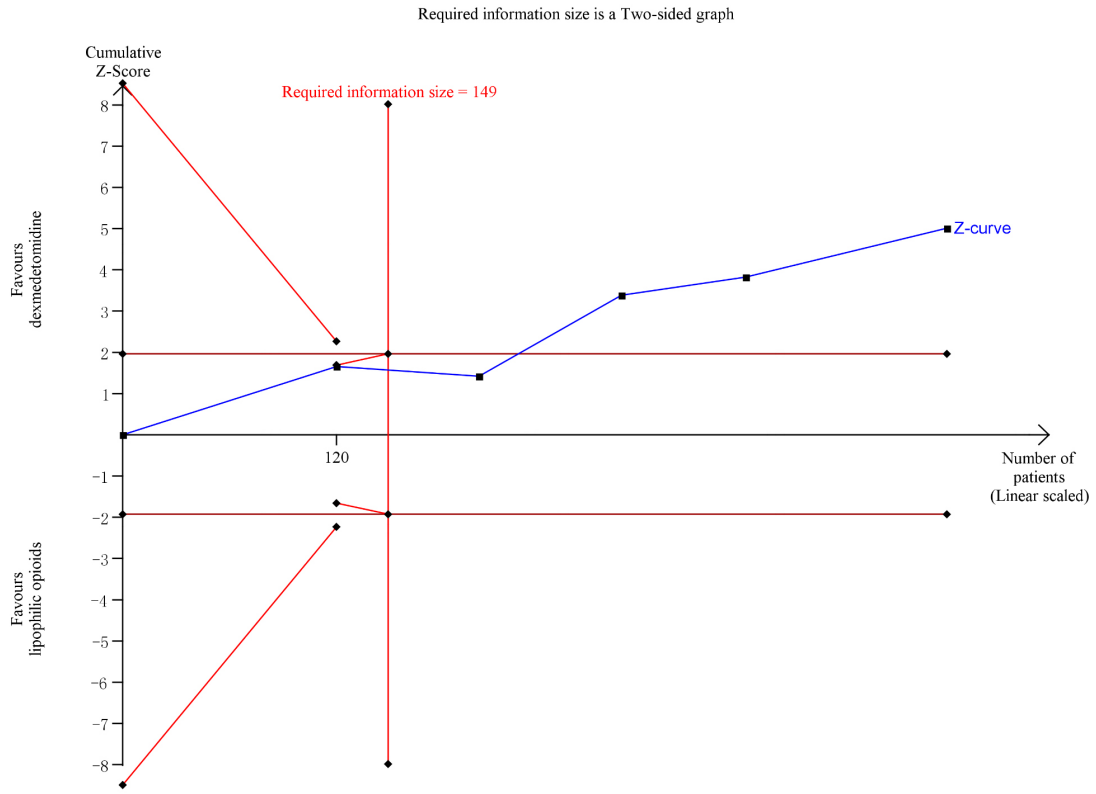

FIGURE 5. Trial sequential analysis of duration of second stage of labor.

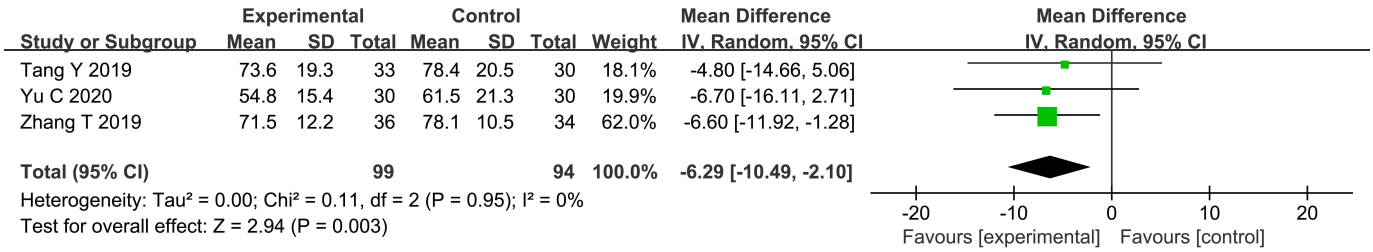

FIGURE 6. Forest plots for the meta-analysis of total analgesic consumption (mL).

TABLE 2. Results of meta-analysis of secondary outcomes.

Parameter	Number of trial	Total cases	Events/Total		WMD/RR [95% CI]	I^2 (%)
			DEX	Control	Significance level	
Maternal hypotension	6	610	31/306	26/304	1.12 [0.48 to 2.65], $p = 0.79$	45
bradycardia	5	530	34/266	12/264	2.44 [1.31 to 4.53], $p = 0.005$	0
nausea and vomiting	10	863	17/435	58/428	0.34 [0.20 to 0.57], $p < 0.0001$	0
pruritis	7	636	1/321	27/315	0.19 [0.06 to 0.58], $p = 0.004$	0
shivering	5	443	9/224	26/219	0.37 [0.18 to 0.77], $p = 0.008$	0
motor blockade	3	293	29/148	5/145	5.30 [2.21 to 12.73], $p = 0.0002$	0
Cesarean delivery rate	9	827	52/415	60/412	0.87 [0.62 to 1.21], $p = 0.40$	0
Instrumental delivery	4	430	8/216	11/214	0.82 [0.33 to 2.07], $p = 0.68$	0
Apgar scores at 1 minute	7	668	337	331	–0.05 [–0.14 to 0.04], $p = 0.24$	5
Apgar scores at 5 minute	6	552	277	275	–0.04 [–0.12 to 0.04], $p = 0.36$	30
Umbilical arterial PH	2	150	76	74	–0.01 [–0.02 to 0.00], $p = 0.16$	0

DEX, dexmedetomidine; WMD, weighted mean difference; RR, risk ratio; CI, confidence interval.

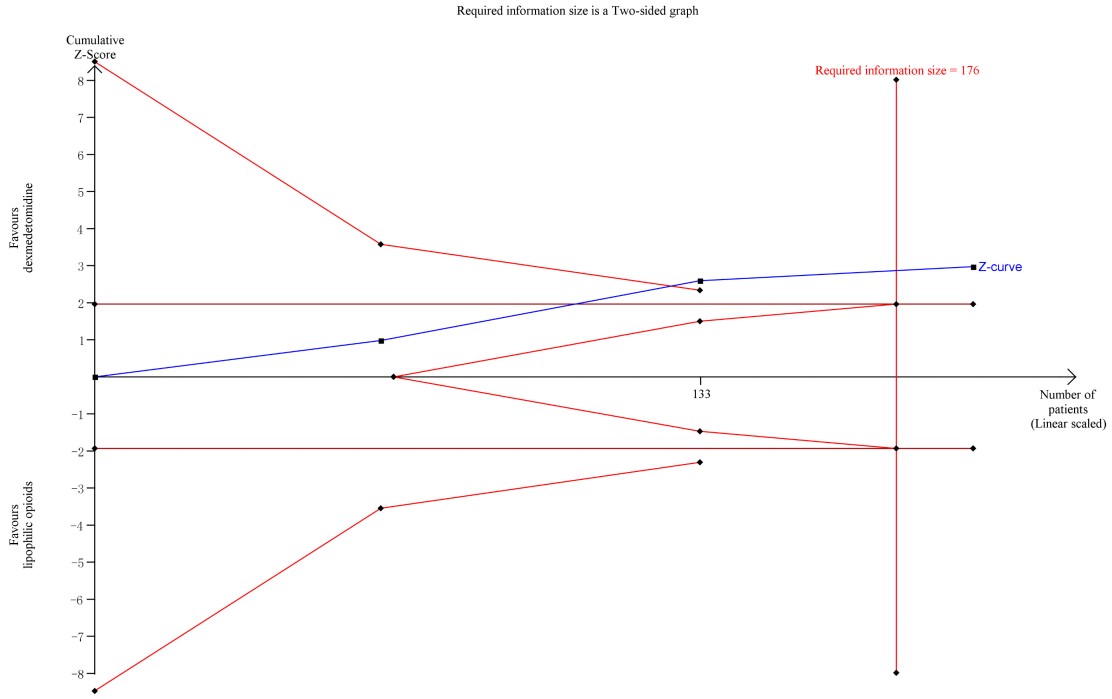

FIGURE 7. Trial sequential analysis of total analgesic consumption.

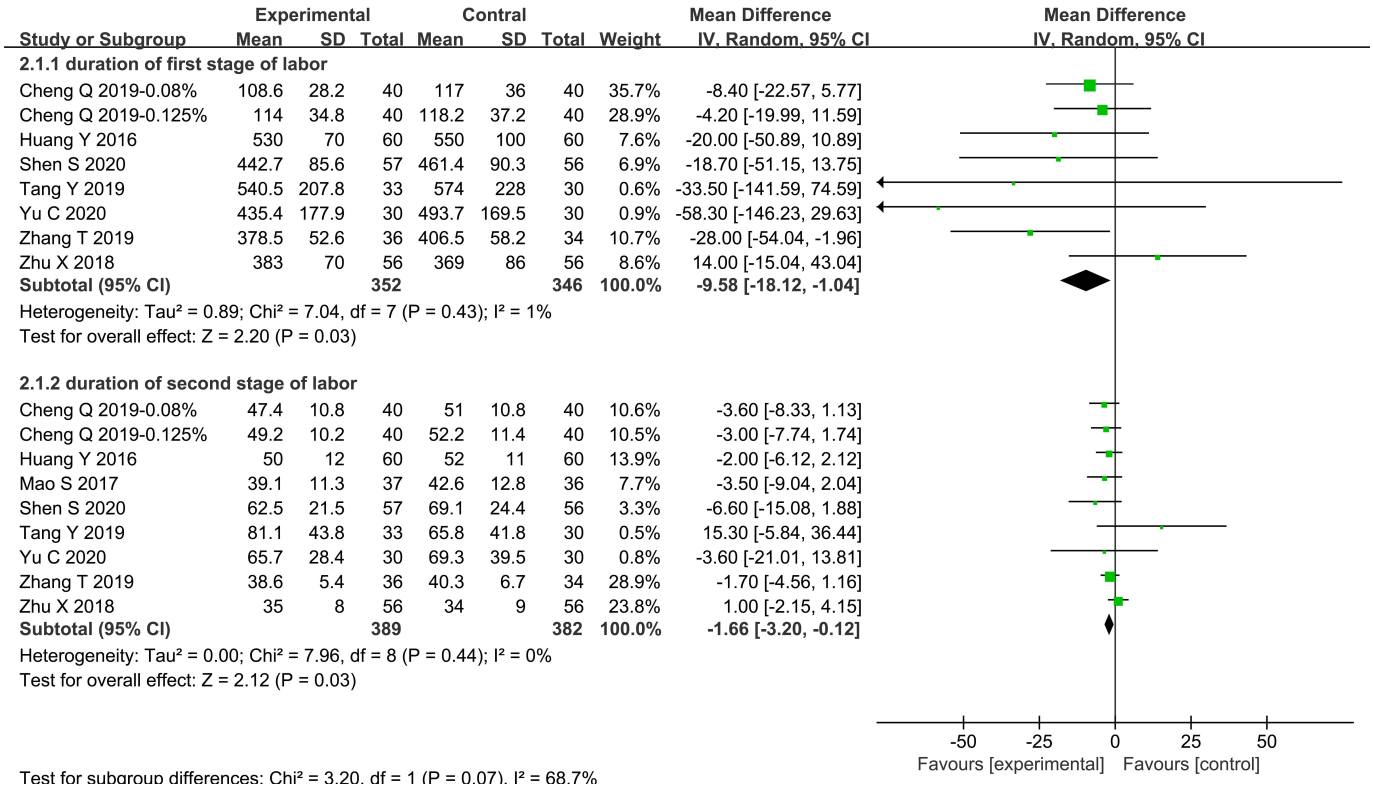

FIGURE 8. Forest plots for the meta-analysis of duration of labor (minutes).

labor [33], the effect of dexmedetomidine on the duration of labor is worthy of further research. Although epidural dexmedetomidine increased the incidence of motor blockade (RR = 5.30, 95% CI: 2.21–12.73), the effect of motor block on delivery may be limited. Motor blockade was mainly observed in parturients that were had an epidural administered by a bolus injection [17, 25], while most of the other studies reported no maternal motor blockade. Moreover, most parturients with motor blockade had a Bromage score of 1, only 1 case showed a score of 2 [17] and none scored more than 2. It also should be noted that the mode of epidural maintenance of labor analgesia with dexmedetomidine had transformed from a bolus injection to a continuous epidural infusion (CEI) and programmed intermittent epidural bolus (PIEB), which decreased the incidence

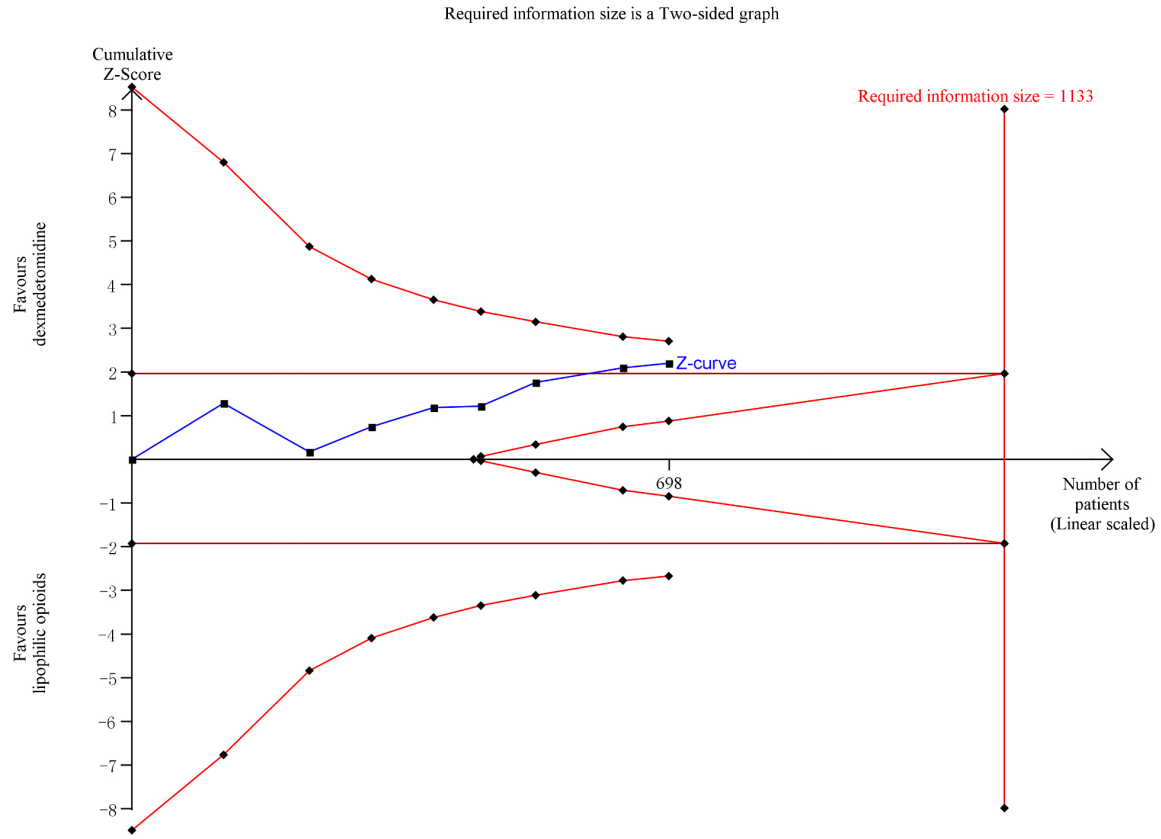

FIGURE 9. Trial sequential analysis for duration of first stage of labor.

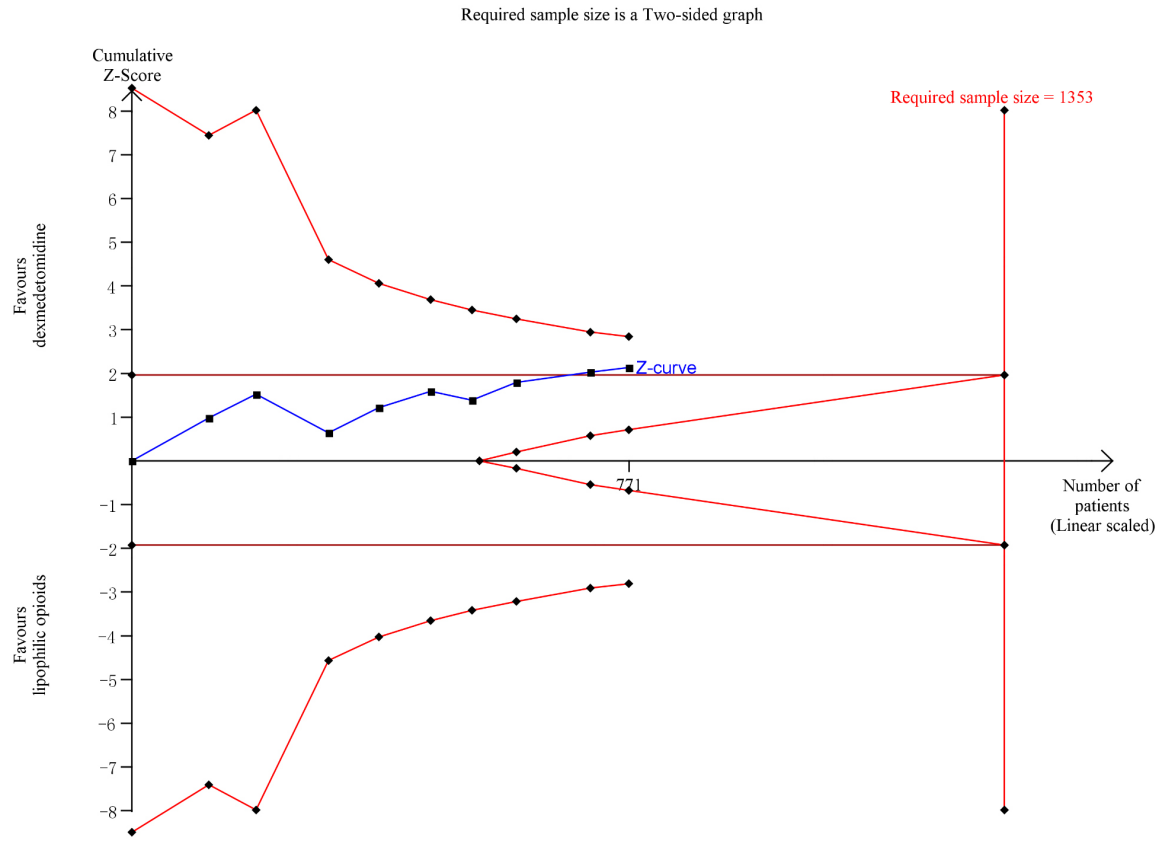

FIGURE 10. Trial sequential analysis of duration of second stage of labor.

of adverse side effects especially maternal bradycardia.

Epidural analgesia appears to be the independent contributor to intrapartum fever. Possible mechanisms include non-infectious systemic inflammation and altered thermoregulation which involve an elevated sweating threshold below the level of the blockade or an increase in the likelihood of heat-producing shivering [34]. But none of the included trials in the meta-analysis reported intrapartum fever, and whether dexmedetomidine can reduce intrapartum fever will require further investigation.

A major concern with neuraxial administration of dexmedetomidine is potential neurotoxicity, although there is no direct evidence of neurological deficit in humans. However, animal studies indicated a possible dose-dependent neurotoxicity [35, 36]. In addition, dexmedetomidine is not licensed for neuraxial use by the FDA and the European Medicines Agency (EMA), and needs an Investigational New Drug (IND) approval before use.

There are some limitations in our meta-analysis. First, the number of studies meeting the inclusion criteria was limited, and most of the included RCTs had small sample sizes. Second, there was significant heterogeneity in the regimens and concentrations of local anesthetics used, in addition, the total amount of administered drugs was also not clearly stated in most included studies. Different doses and number of boluses of analgesics administered to perform analgesia could also have an impact on some outcomes. Third, all included studies were conducted in several countries leading to publication bias, and possibly limiting the generalization of our findings. Lastly, the certainty of evidence in most of outcomes was downgraded due to the heterogeneity and potential publication bias, and should be interpreted with caution.

5. Conclusions

In summary, compared with lipophilic opioids, dexmedetomidine could provide a similar analgesic effect but reduced analgesic agent consumption when used as adjuvants to local anesthetics for epidural labor analgesia, and reduced maternal nausea and vomiting, pruritis, shivering, but increased maternal bradycardia, and may shorten the duration of labor. A larger sample size and more high-quality RCTs world-wide are required to confirm these findings.

AUTHOR CONTRIBUTIONS

SKY and WQS designed the study. YYY and FZZ collected related paper. ML, JC and DZM performed data extraction and statistical analyses. SKY, ML and JC drafted and revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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