Meta-Analysis

Effectiveness of Remifentanil for Labor Pain Control
A Systematic Review and Meta-Analysis

Zhaohui Wang, MD, MSc; Shiqin Xu, MD, MPH; Xiaofeng Shen, MD, MPH; Shan-Wu Feng, MD, PhD

BACKGROUND  Many medical conditions restrict the use of neuraxial analgesia for labor pain control, and several options such as hypnosis, acupuncture, entonox and doula have limited efficacy. Intravenous remifentanil patient-controlled analgesia (PCA) is being considered as the potential alternative to epidural analgesia (EA) and assessed by several studies. The aim of this study was to systematically assess the effectiveness of intravenous remifentanil patient-controlled analgesia (PCA) for the relief of labor pain and the influence on maternal and infant outcomes.

METHODS  Electric databases and clinical guidelines were searched. Two reviewers independently evaluated the relevance, inclusion and study quality, and extracted the data of randomized controlled trials in which i.v. remifentanil PCA were compared with any other analgesic treatment for labor pain in healthy parturients. Weighted mean differences and odds ratio were calculated and are reported with 95% confidence intervals.

RESULTS  From 105 potentially relevant titles and abstracts, seven studies, of variable methodological quality, were included. All included trials used i.v. remifentanil PCA technique and compared with different pain-alleviating means, examining analgesic efficacy from 30 min to over 11 h. Remifentanil provided superior analgesic effect than the comparison (weighted mean difference -1.82, 95% confidence interval -2.12 to -1.53), but produced negative influence on the infant outcomes (Odds Ratio 0.10, 95% confidence interval 0.03 to 0.42). Delivery methods and side effects were similar between remifentanil and the comparison.

CONCLUSIONS  Pooled assessment of remifentanil intervention seems an attractive strategy for controlling labor pain in health term parturients, but it is not supported by strong evidence. Current evidence suggests that it may produce effective analgesia by only a modest level.

KEYWORDS  Remifentanil; Labor Pain; Labor Analgesia; Systemic Analgesia; Meta-Analysis


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The use of epidural analgesia (EA) is recommended as an optimal means in labor pain control by the clinical guideline (1), whereas in some medical conditions including spinal abnormalities, bleeding tendency, infection, allergic to local anesthetics, maternal anxiety to EA procedure and lack of epidural puncture experience at some centres as well, the EA technique cannot be performed successfully, under which an alternative to EA is demanded. Several options such as hypnosis (2), acupuncture (3), entonox (4), doula (5), yoga (6) and transcutaneous electrical nerve stimulation (7) have been used for labor analgesia, but the analgesic efficacy of these methods is limited and inconsistent. Besides these, systemic administration of opioids has been considered as the potential offer to EA, and thus pethidine and fentanyl were used at early time. However, these two drugs were discarded for their high incidence of maternal and infant side effects and inadequate analgesia (8, 9). Therefore, how to conquer these drawbacks and realise optimal analgesia by one drug delivered systemically is searched and found that remifentanil is likely to be the option.

Remifentanil, a newest ultra-short acting mu opioid agonist, is a piperidine derivative with the normal opioid configuration, but contains an ester linkage being susceptible to non-specific esterases and independent of hepatic and renal function (10), and has a context-sensitive half-time of 3 min, and quickly redistributed and metabolised in the fetus (11). Thus it is widely regarded as a safe and ideal analgesic in systemic administration for labor alleviation due to its “easy come, easy go” characteristic (12-14).

Generally, one major concern of i.v. administration of drugs during labor is the trans-placenta characteristic strongly associated with fetus status, especially the increase in the rate of intraplacental depression and post-partum resuscitation (15). Although remifentanil can pass through the blood-placenta barrier, its short half-life time and quick distribution and metabolism determine that remifentanil will not cumulate in fetuses. In addition, the clinical feasible property of maternal monitorings guarantees remifentanil’s potential use. To date, several studies with respect to the i.v. remifentanil PCA in labor pain control have been done, whereas the actual effect of remifentanil is inconsistent because the sample size was small, and the interventional strategies were inconsistent each other (16-25). It is intriguing to clinical practice and further research to combine these studies together and analyze the role for remifentanil in labor analgesia.

Materials and Methods

Criteria for Considering Studies for This Review
Randomized controlled trials were enrolled in this meta-analysis. Healthy term parturients, nulliparous or multiparous, requesting labor pain control were selected as the study subjects. The interventions were i.v. remifentanil PCA vs. other analgesic means. Continuous and dichotomous outcomes were analyzed in this study. The primary outcome of interest was the analgesic efficacy rated with a 0-10 cm visual analogue scale (VAS). Secondary outcomes considered were the delivery methods (cesarean or instrumental), the maternal side effects and infant outcomes associated with the treatment.

Search Methods for Identification of Studies
The search carried out using the search terms "remifentanil", "labo(u)r", "labo(u)r pain", "analgesia", "labo(u)r analgesia", "patient-controlled analgesia" or "PCA". In the Medline and EMBase databases, randomized studies were identified by limiting these studies to "randomized controlled trial", "Multicentre study", "controlled clinical trial" or "clinical trial". The following databases were searched: Medline (1966-2015; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB = PubMed), EMBase (1988-2015; www.embase.com), and the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html, with the search carried out on July 30 2015). LILACS, CINAHL, ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBMdisc), China National Science & Technology Library (NSTL), WanFang Data were searched too. Corresponding authors were contacted to obtain additional information if necessary. We did not search the conference proceedings. Language of publication and non-publication were not reasons for exclusion.

Data Collection and Analysis
Information on patients, methods, interventions, outcomes, and side effects was extracted from the original reports on to specially designed forms by at least three independent reviewers (SF, ZW). Disagreements were

**Selection of Studies**

Studies met the following four criteria were included: study design (randomized controlled trial), study population (healthy term parturients), intervention (i.v. remifentanil PCA vs. control (non-remifentanil or non-epidural analgesia)), and availability of outcome data on analgesic efficacy, maternal and infant outcomes. Two independent reviewers (SF and ZW) screened the titles and abstracts of eligible studies. Potentially relevant papers were obtained and two independent reviewers (SF and ZW) reviewed the full manuscripts for possible inclusion. Disagreements were resolved by consensus.

Non-standard designs of studies such as cross-over trials were excluded from the present review for its special and complicated demand of analyzes and the possibility of bias induction (26). In addition, we combined the remifentanil intervention groups of the study with multiple treatment groups to create a single pair-wise comparison (20) and then compared with the control one. In addition, if the comparison was remifentanil or epidural analgesia, we excluded them because such control group would make the conclusion unsuitable for explaining the potential role for remifentanil in labor analgesia. Besides, epidural analgesia itself has a superior effect on labor pain control than systematic analgesia (1), and then the study was precluded if the comparison was used epidurally.

**Assessment of Risk of Bias in Included Studies**

We assessed the internal validity of individual trials using Jadad’s scale (26) by at least three reviewers independently (SF, ZW), which evaluates the reported randomization, blinding, and withdrawals in a clinical trial.
<table>
<thead>
<tr>
<th>Reference (Country)</th>
<th>Design</th>
<th>No. of participants</th>
<th>Setting of investigators</th>
<th>Eligibility criteria</th>
<th>Population characteristics</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Observation period of Analgesia (h)</th>
<th>Trial quality</th>
<th>Randomization described, appropriate</th>
<th>Blinding described, appropriate</th>
<th>Losses to follow-up described</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volikas 2001 (UK)</td>
<td>RCT</td>
<td>17</td>
<td>Department of Anaesthesia</td>
<td>ASA I/II; with no known obstetric complications; requesting pethidine analgesia</td>
<td>Healthy women; 23-34 years; 36-40 weeks gestation; 52.9-105.2kg in weight; mixed parity; initial cervical dilation of 3-6 cm</td>
<td>i.v. Remifentanil PCA, bolus of 0.5 μg/kg, lockout period of 2 min, no hourly maximum limit</td>
<td>i.v. Pethidine PCA, bolus of 10 mg, lockout period of 5 min, maximum limit of 100 mg/h</td>
<td>11 h</td>
<td>Yes, no</td>
<td>Yes, yes</td>
<td>No</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Thurlow 2002 (UK)</td>
<td>RCT</td>
<td>36</td>
<td>Department of Anaesthesia</td>
<td>N/A</td>
<td>18-40 years; 38-42 weeks gestation; 50-100 kg in weight; mixed parity; initial cervical dilation of 3-5 cm</td>
<td>i.v. Remifentanil PCA, 20 μg loading dose, lockout period of 3 min, no background infusion</td>
<td>Meperidine 100 mg i.m.</td>
<td>Over 120 min</td>
<td>Yes, yes</td>
<td>No, no</td>
<td>Yes</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Blair 2005 (UK)</td>
<td>RCT</td>
<td>39</td>
<td>Department of Anaesthesia</td>
<td>ASA I/II; either before the onset of labor or in early labor before any analgesia</td>
<td>19-39 years; 57-105kg in weight; mixed parity; initial cervical dilation of 2-8 cm</td>
<td>i.v. Remifentanil PCA, bolus of 0.5 μg/kg, lockout period of 2 min, 1-ml bolus over 18 s</td>
<td>i.v. Pethidine PCA, bolus of 15 mg, lockout period of 10 min, 1-ml bolus over 18 s</td>
<td>35-330 min</td>
<td>Yes, yes</td>
<td>Yes, no</td>
<td>Yes</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Evron 2005 (Israel; USA)</td>
<td>RCT</td>
<td>88</td>
<td>Department of Anaesthesia; Outcomes Research™ Institute</td>
<td>ASA I/II; singleton cephalic presentation; requesting systemic analgesia</td>
<td>24-35 years; 60-95kg in weight; mixed parity; initial cervical dilation of 3-6 cm</td>
<td>i.v. Remifentanil PCA, 20 μg loading dose, lockout period of 3 min; The dose was increased every 15-20 min by 5-μg, to a maximal limit of 1500 μg/h. If any parturient had reached the limit, a single bolus 70 μg (0.93 μg/kg) used for inadequate analgesia</td>
<td>75 mg of meperidine in 100 ml of saline over 30 min (1 mg/kg in a single bolus). Another dose of 75 mg followed by 50 mg was administered, (maximum dose of 200 mg) for insufficient analgesia</td>
<td>Till the end of the first stage of labour</td>
<td>Yes, yes</td>
<td>Yes, yes</td>
<td>No</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Jing 2007 (China)</td>
<td>RCT</td>
<td>65</td>
<td>Department of Anaesthesia</td>
<td>Full-term pregnant women; ASA I/II; singleton cephalic presentation; no oxytocin use; no obstetric complications</td>
<td>24-35 years; 38-42 weeks gestation; 59-90kg in weight; nulliparas</td>
<td>i.v. Remifentanil PCA, bolus of 0.5 μg/kg, lockout period of 3 min, with or without background infusion 0.05 μg/(kg min)</td>
<td>Doula support</td>
<td>Till delivery completed</td>
<td>Yes, no</td>
<td>No, no</td>
<td>No</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Characteristics of Included Studies Investigating the Analgesic Efficacy of Remifentanil in Labor Pain Control, Ordered by Publication Date (continued)

<table>
<thead>
<tr>
<th>Reference (Country)</th>
<th>Design</th>
<th>No. of participants</th>
<th>Setting of investigators</th>
<th>Eligibility criteria</th>
<th>Population characteristics</th>
<th>Treatment</th>
<th>Comparison</th>
<th>Observation period of Analgesia (h)</th>
<th>Trial quality</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng 2011 (Hong Kong SAR)</td>
<td>RCT</td>
<td>68</td>
<td>Department of Anaesthesia and Intensive Care</td>
<td>Full term parturients; ASA I/II; singleton pregnancy; cephalic presentation; in the first stage of spontaneous labour; requested parenteral opioid for labour Analgesia; no complicated obstetric history</td>
<td>23-34 years; 37-41 weeks gestation; 59.1-79.3 kg in weight; mixed parity; initial cervical dilation of 0-4 cm</td>
<td>i.v. Remifentanil PCA, bolus of 25 μg in 1.25 ml for parturients weighing &lt; 60 kg and 30 μg in 1.5 ml for those weighing ≥ 60 kg, bolus rate of 20 ml·h⁻¹, lockout period of 3.75-4.50 min, to a maximal limit of 500 μg/h, no background infusion</td>
<td>A single intramuscular injection of pethidine 50 mg diluted to 1.5 ml with saline to parturients weighing &lt; 60 kg and pethidine 75 mg in 1.5 ml to those weighing ≥ 60 kg</td>
<td>Till delivery completed</td>
<td>Yes, yes</td>
<td>Yes, yes</td>
</tr>
<tr>
<td>Muñoz 2014 (Spain)</td>
<td>RCT</td>
<td>60</td>
<td>Department of Anaesthesia and Resuscitation</td>
<td>ASA I/II; non-cephalic presentation; requested external cephalic version</td>
<td>27-39 years; 36-41 weeks of gestation; 23.7-31.1 kg/m² in body mass index; mixed parity</td>
<td>i.v. Remifentanil infusion at 0.1 μg/kg/min, demand boluses of 0.1 μg/kg, lockout period of 4 min</td>
<td>Saline placebo.</td>
<td>10 min after finishing the procedure</td>
<td>Yes, yes</td>
<td>Yes, yes</td>
</tr>
</tbody>
</table>
and assigns a score from 0 to 5, with higher scores indicating higher quality in the conduct or reporting of the trial. Studies were not excluded on the basis of methodological quality of trials, but this information was used in the sensitivity analysis.

**Measures of Treatment Effect**
Analgesic efficacy of i.v. remifentanil PCA and corresponding control intervention was rated with a 10-cm linear Visual Analogue Scale (VAS) system, and such scorings were treated as the continuous data analyzed with the mean and standard deviation (SD) presented as mean difference (MD) and 95% confidence interval (95% CI). Other measures including the delivery methods (cesarean or instrumental), side effects of drug delivery and infant outcomes were presented as the dichotomous variables and analyzed using odds ratio (OR) and 95% CI.

**Dealing with Missing Data**
In avoiding missing whole studies because they are never published, are published in obscure places, are rarely cited, or are inappropriately indexed in databases, we searched almost all-can-be-gotten electric databases comprehensively without limitation of the publication language. However the conference proceedings were not searched. Regarding the missing outcome, missing summary data of an outcome, and missing participants, we contacted the original investigators by mails to request these missing data, only if such action was failed, we did assumption about their relationships with the available data by treating them as if they were observed and all were poor outcomes, and then intention-to-treat (ITT) analyzes were performed, as appropriate.

**Assessment of Heterogeneity**
The Chi-square test and I² statistic were used in the present review to measure the heterogeneity (0% to 40%: not be important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity) (27, 28). A P value of less than 0.10 is used to determine statistical significance.

**Assessment of Reporting Biases**
Although the rank correlation between standardized intervention effect and its standard error was recommended to measure the asymmetry of funnel plot as described elsewhere (29), given only seven studies were included in the present review. Therefore, the assessment of reporting biases was performed, though, the data were not presented.

**Data Synthesis**
We pooled and presented the results of studies using fixed-effect model. If the heterogeneity among trials was considerable, then the random-effect model would be used as the post hoc test of heterogeneity. For dichotomous variables we calculated individual and pooled statistics as Odds Ratio with 95% CIs. For continuous outcomes the mean differences reported from individual trials were calculated, and the weighted mean differences with associated 95% CIs were pooled. The Mantel-Haenszel method for dichotomous outcomes or the inverse variance method for continuous outcomes was used.

**Subgroup Analysis and Investigation of Heterogeneity**
Subgroup analyzes were carried out to detect the heterogeneity, the primary outcome was stratified by different control interventions and in different participants (nulliparity vs. mixed parity), and the secondary outcomes were subgrouped according to different observational measures. We performed tests for heterogeneity using the Mantel-Haenszel or inverse variance methods.

**Sensitivity Analysis**
Sensitivity analyzes were performed by repeating the primary analysis or meta-analysis with subgroup analyzes, alternative use of fixed-effect or random-effect model, and different selection of outcome presentation including ORs, risk ratios (RRs), risk differences (RDs), MDs or standardized mean difference (SMDs) for substituting alternative decisions or ranges of values for decisions about the analgesic efficacy of i.v. remifentanil PCA in labor pain control.

**Results**

**Description of Studies**
Two reviewers determined independently the studies' inclusion or exclusion. The initial search for studies involving remifentanil treatment of labor pain control yielded 105 articles, of which 12 were potentially eligible on the basis of their title and abstract.

**Included Studies**
Figure 2: Meta-Analysis of pain intensity among those on remifentanil compared with controls*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Remifentanil</th>
<th>Comparison</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total Mean</td>
</tr>
<tr>
<td>Volkas 2001 [16]</td>
<td>4.4</td>
<td>2.9</td>
<td>9</td>
</tr>
<tr>
<td>Thurlow 2002 [17]</td>
<td>6.7</td>
<td>1.1</td>
<td>18</td>
</tr>
<tr>
<td>Evron 2005 [19]</td>
<td>6.4</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>Blair 2005 [18]</td>
<td>3.4</td>
<td>0.9</td>
<td>43</td>
</tr>
<tr>
<td>Jing 2007 [20]</td>
<td>4.9</td>
<td>2.2</td>
<td>42</td>
</tr>
<tr>
<td>Ng 2011 [21]</td>
<td>3.5</td>
<td>2.2</td>
<td>34</td>
</tr>
<tr>
<td>Muñoz 2014 [22]</td>
<td>4.7</td>
<td>2.5</td>
<td>31</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>197</td>
<td></td>
<td>176</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 10.48, df = 6 (P = 0.11); I² = 43%
Test for overall effect: Z = 12.11 (P < 0.00001)

*: The green squares represent the effect estimates of remifentanil; the black lines represent the 95% confidence intervals associated with the effect estimates. The black diamonds represent the summary effect estimates for the overall effect (total).

Seven studies that met the four inclusion criteria were analyzed (16-22). These studies were carried out in five countries or areas (three from the United Kingdom, one from Israel and the United States of America, one from China, one from Hong Kong SAR, and one from Spain) (Table 1). Total of 373 parturients aging from 18 to 40 years were studied: 197 parturients assigned to i.v. remifentanil PCA and 176 assigned to other analgesic treatments. Of the seven studies, five studies used meperidine (pethidine) as the control group (16-19, 21), one used Doula support (20), and one used saline (22). Six studies enrolled mixed parity, and one study performed only in nulliparous women. Three studies investigated the singleton cephalic presentation, one investigated the non-cephalic presentation, and three others were not clear (Table 1). One study did not provide any eligibility criteria for participant’s enrolment (17).

The regimen of i.v. remifentanil PCA was of the bolus doses of 0.50 μg/kg in three studies, of which one used two intervention arms with or without basal infusion and combined as a single comparison, and three studies gave a 15 μg to 30 μg bolus dose of which one delivered remifentanil with a step-wise increase of 5 μg to a maximal limitation of 1500 μg/h, one to a maximal limit of 500 μg/h. One study infused remifentanil at 0.1 μg/kg/min and a demand bolus of 0.1 μg/kg. Of the included studies, two studies described that a loading dose of 20 μg was given, but others were not available about the loading dose information (Table 1).

The follow-up period after remifentanil PCA initiated was variable, ranging from 30 min to over 11 h. Two study mentioned that the follow-up ceased till the delivery complete (19, 21), one to the end of the first stage of labor (19), and one 10 min after finishing external cephalic version (22), and one study followed-up over 10 h (16) and other two studies observed merely 0.5-5 h (17, 18) (Table 1).

Excluded Studies
Of the 105 articles examined, we excluded 28 studies as merely the review article, ten studies were case reports, and twelve studies appeared as the editorial or editor’s opinion, seven studies was letters without original data, and seven reports were correspondences, fifteen study used epidural analgesia as the control, five studies without the comparison, three studies performed using an animal, and one duplicated publication, four study designed with a crossover manner that is difficult to be analyzed for its special and complicated requirements of assessment, and two trial listed as ongoing in the ClinicalTrials.gov could not be found as published reports and therefore were not considered, and four studies have been done only for finding an optimal dose of remifentanil without a control group provided (Fig. 1).

Risk of Bias in Included Studies
The methodological quality of the studies assessed with Jadad’s method was variable, with some having major drawbacks. The mean quality score was 3 out of a possible 5.

Allocation
Four of the seven individually randomized studies reported methods of random allocation that had secure allocation concealment. The other three merely stated that allocations were concealed but gave no further details or did not report sufficient information or used insecure methods.

Blinding
Although blinding of participants and staff delivering the interventions was generally difficult, five studies described the blinding methods with a secure way. Three studies achieved blinding of care, two of them provided detailed description of the allocation and one did not. The other two studies did not report the blindness of the care delivery and outcome assessment.

Incomplete Outcome Data
Six studies reported losses and exclusions of randomized participants by the end of follow-up. Intention-to-treat analysis was adhered to in one study.

Other Potential Sources of Bias
In avoiding bias of study searching, various databases were retrieved. We did not search the conference proceedings, and did not contact any pharmaceutical entities and experts on remifentanil.

Effects of Interventions
Analgesic Efficacy
Among those on remifentanil, compared with those assigned to different analgesic methods, i.v. remifentanil PCA appeared to display better analgesic efficacy than other comparisons, the mean difference of pain intensity scaled with linear VAS gauge was \(-1.82\) (95% CI: \(-2.12\) to \(-1.53\)). Among those assigned to meperidine (pethidine) as the control group in five studies (16-19, 21), the analgesic efficacy of i.v. remifentanil PCA was better than the meperidine control, the mean difference was \(-1.80\) (95% CI: \(-2.12\) to \(-1.48\)). One study used Doulga support and one employed saline placebo as the con-
trol comparison (20), and the analgesic efficacy of remifentanil were superior than those assigned to control (Fig. 2). We did not do analgesic analyses restricted to different follow-up periods due to complicated influence of different control interventions.

### Delivery Methods

We pooled studies providing data of delivery methods. Data on cesarean delivery were available for six studies (16, 17, 19-22). Among those on i.v. remifentanil PCA,
compared with those assigned to control comparisons, remifentanil did not reduced the odds of cesarean section of what they were in the control group (95% CI: 0.47 to 1.50). Data on instrumental delivery were available for six studies (16, 17, 19-22). The odds of instrumental delivery in control comparisons was not reduced compared with the remifentanil treatment, the OR was 1.36 (95% CI: 0.66 to 2.80). After pooled the delivery methods together, the odds in remifentanil was not increased than those assigned to different controls, the OR was 1.02 (95% CI: 0.65 to 1.59). (Fig. 3).

Side Effects
Data on side effects were available from six studies (16, 17, 19-22). Side effects were reported in 69 out of 367 patients (18.8%) allocated to i.v. remifentanil PCA and in 68 out of 324 patients (21.0%) allocated to control. Nausea and vomiting were reported in 18 out of 177 parturients allocated to remifentanil (10.2%) and 22 out of 157 parturients allocated to control comparisons (14.0%), and the remifentanil treatment had less odds in reducing nausea and vomiting compared with the control, the OR was 0.69 (95% CI: 0.35 to 1.36). Itching was reported in five women out of 42 allocated to remifentanil (11.9%) and zero allocated to the control (20), and the remifentanil did not reduce the odds of itching versus the control, the OR was 6.89 (95% CI: 0.36 to 130.47). During the administration of remifentanil, supplemental oxygen was used when the saturation of oxygen (SaO₂) was less than 95%, i.e. the hypoxemia due to respiratory depression. In the study reported supplemental oxygen use (17), 7 out of 18 patients allocated to remifentanil (38.9%) and 2 out of 18 patients allocated to the control ones (11.1%) were given additional oxygen, and the remifentanil did not increased the odds of supplemental oxygen use than those in the control group, the OR was 5.09 (95% CI: 0.89 to 29.27). Dizziness and drowsiness were reported in 35 out of 65 parturients allocated to remifentanil (53.8%) and 34 out of 63 parturients allocated to control comparisons (54.0%), and the remifentanil did not increased the odds of dizziness and drowsiness compared with the control, the OR was 1.63 (95% CI: 0.21 to 12.65). Abnormal fetal heart rate tracings were reported in 4 out of 65 allocated to remifentanil (6.2%) and 10 out of 63 allocated to the control (15.8%), and the remifentanil did not reduce the odds of abnormal fetal heart rate tracings versus the control, the OR was 0.32 (95% CI: 0.09 to 1.10). Generally, i.v. remifentanil PCA had less odds in decreasing side effects compared with the control, the OR was 0.90 (95% CI: 0.54 to 1.47) (Fig. 4).

Infant Outcomes
Data on infant outcomes associated with drug administration were available for two studies (16, 20). One-min Apgar score ≤ 7 was reported in one out of 51 infants allocated to remifentanil (1.9%) and eight out of 31 infants allocated to the control (25.8%), and the remifentanil reduced the odds by 91% of what they were in the control group, the OR was 0.09 (95% CI: 0.02 to 0.50). Data of the incidence of five-min Apgar score ≤ 7 or the rate of resuscitation of infants have been reported in only one study (16). However, the overall meta-analysis of infant outcomes displayed that the remifentanil reduced the odds of still being in negative outcomes to 10% of what they would have been, the OR was 0.10 (95% CI: 0.03 to 0.42) (Fig. 5).

Sensitivity Analysis
There were not any important changes in the estimates when the analysis was restricted to studies on nulliparous or mixed-parous populations, or studies that used meperidine, Doula or saline as the control groups, or studies that met all the indicators of methodological quality.

Considerable heterogeneity was found in the analyses of side effects (I²=47%) and one-min Apgar score ≤ 7 (I²=68%), which were explored using subgroup analyses. Additionally, no changes in the overall estimates were found when using the random-effects method. When examining studies reporting analgesic efficacy overall, the smallest P-value for tests of homogeneity was < 0.00001. Results from studies reporting differences in side effects were disparate; the P-value for test of homogeneity was 0.03. Data reporting infants’ one-min Apgar score ≤ 7 were examined and the P-value for test of homogeneity was 0.08. All these estimates were still statistically significant when using the random-effects method with the sub-analyses. We sub-analyzed the analgesic efficacy in the studies that meperidine was use as the control only, though substantial heterogeneity was found (χ²=10.32, df=4, P=0.04, I²=61%), a better analgesia was displayed. This is consistent with the idea that remifentanil intervention may be more effective than meperidine but still needs testing in future studies.

Discussion
Summary of Main Results
The results of the seven studies included in this systematic review showed that remifentanil appears to be effective in controlling labor pain when used intravenously with PCA technique. Compared with parturients performed other analgesic means, those who were randomized to remifentanil have a better analgesic efficacy without increasing the odds of cesarean and instrumental delivery and the maternal incidence of side effects, but the odds of infants' negative outcomes are much higher. For some outcomes the results were heterogeneous, investigation of these in subgroups analyzes showed no significant differences in analgesic effectiveness between remifentanil and meperidine or Doula and between populations only in nulliparity and unselected populations in mixed parity.

Overall Completeness and Applicability of Evidence
While the present analysis suggests that benefits from this type of intervention of remifentanil is obvious as previously supposed, several aspects limiting the completeness of such conclusion should be acknowledged. This conclusion is mainly based on the analysis of the pain intensity ratings with the VAS system, which was the most commonly reported outcome. We were unable to synthesize and analyze data of the pain relief scoring and effective analgesic number of patients of which did not reported by the included studies. Therefore, it is possible that the VAS ratings of pain alone were not strong enough as the evidence to draw the above conclusion. More importantly future studies need to be done to show whether similar changes occurred in the outcomes of the pain relief scoring and the effective analgesic number of patients. Furthermore, of the seven included trials, no one study completely reported all outcomes analyzed in this review and no two studies used identical intervention strategy. Thus the individualized interventions in each study and the discrepant report of outcomes resulting in a lack of consistency in
outcome measures, these are probably the critical factors restricting our ability to combine results across many trials and consequently influencing the correctness of the conclusion. So this review should be evaluated with the above limitations in mind.

Quality of the Evidence
The overall quality of the evidence was not high. Most of the trials were small and many had methodological drawbacks leaving them open to bias, such as insecure allocation concealment, lack of blinding of outcome assessment and poor reporting. A major limitation of the existing evidence is the lack of data on reporting the number of patients with inadequate analgesia. This is usually the main factor affecting the distribution of the important outcome. Failure of analgesia is too popular to be ignored. Epidural labor analgesia had a rate of 5.3-19.7% of inadequate pain control (30), but none of the included studies reported the rate of inadequate analgesia with i.v. remifentanil PCA. Further trials are needed that record such important outcome to allow analysis of analgesic efficacy.

Potential Biases in the Review Process
Although there was evidence of heterogeneity for some outcomes, we could not account for the observed heterogeneity in several subgroup analyzes. Despite this heterogeneity, both fixed-effects and random-effects summaries were consistent with beneficial effects of i.v. remifentanil PCA in the overall estimates. The heterogeneity suggests the size of the benefit varies by some other factors that we were not able to identify.

Methodological heterogeneity is also likely to have played a role in the observed statistical heterogeneity. Studies were carried out in several countries and differences between the populations or the experimental interventions or the control comparisons might have contributed to the heterogeneity. The variable risk of bias of the included studies may have result in variation in the estimates of treatment effect. In addition, different durations of follow-up may have led to heterogeneity of effect estimates. Three of the seven studies reported follow-up period at least till the end of the delivery, and four with shorter durations. A reduction of heterogeneity was found in the longer-lasting trials after sub-analyses, but it was still substantial. However, in the shorter-duration studies, the heterogeneity was far more significant ($I^2=70\%$). Finally, selection bias is always possible. To minimize the likelihood of such bias, two independent reviewers screened all abstracts and primary manuscripts by using standardized eligibility criteria.

Although side effects were reported in some studies, they mainly focused on nausea and vomiting, and only two study evaluated side effects in a relative all-around manner. In addition, randomized controlled studies may not be the best way to determine the incidence of side effects. Given healthy pregnant women were selected as the studying population, so those with obstetric complications were excluded from these trials, as thus remifentanil should probably not be used in that population. In addition, parturients with moderately/severely side effects during remifentanil administration might have been dropped out and resorted to EA instead. Therefore, caution should bear in mind when assessing the conclusion of this review.

Agreements and Disagreements with Other Studies
Of the total included trials in the present review, the populations enrolled in each individual study were healthy parturients and they could be transferred to perform EA if remifentanil analgesia was inadequate. The primary purpose of this intervention was to clarify whether i.v. remifentanil PCA were alternative means when the performance of EA technique was limited by many medical conditions, thus healthy women were not representative populations for such consideration. Studies focused on those with EA contraindications are rare, whereas several case reports presented the successful administration of remifentanil in these populations. To date the available data showed that seven women with platelet abnormalities (31-33), five women with sepsis (32, 34), one woman with epidural refusal (32), one woman with sacral agenesis (34), one woman with von Willebrand’s disease (35), one woman with thrombocytopenia and renal insufficiency (36), and one woman with multiple sclerosis (37) used i.v. remifentanil PCA successfully without obvious sequelae. It would be more efficient for drawing the conclusion of remifentanil administration if trials designed on this population, and if systematic reviews used such patients’ data to allow more accurate and standardized handling of the data from the specialized parturients.

Implications for Practice
Pooled assessment of remifentanil intervention seems an attractive strategy for controlling labor pain in health term parturients, but it is not supported by strong evidence. Current evidence suggests that it may produce
effective analgesia by only a modest level. Evidence of its effects on other outcomes including the rating of pain relief, number of people with inadequate analgesia, and satisfaction with analgesia is insufficient. The costs of implementation of these interventions have not been extensively studied but as they are likely to be expensive, the cost effectiveness of this type of intervention is questionable. In nulliparous or multiparous women, the effect of remifentanil intervention may be distinct, so the selection of enrolled population needs weighing carefully.

**Implications for Research**

Few large scale, high quality randomized controlled trials have yet been carried out. Studies are needed that are powered to detect clinically important effects on the pain intensity, rating of pain relief, number of people with inadequate analgesia, and satisfaction with analgesia, to resolve the uncertainty about the clinical effectiveness and cost effectiveness of this type of intervention. If these definitions and outcomes were used consistently across studies on labor pain control, studies would be more amenable to being summarized with meta-analysis technique. Further research is required to determine whether specific patient subgroups are more likely to benefit from this treatment. In order to enhance the rate at which evidence becomes available and is translated into clinical guidelines, future studies would clearly benefit from better coordination and cooperation between research groups.

**ARTICLE INFORMATION**

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**REFERENCES**


and neonatal effects. Anesthesiology 1998; 88:1467-1474.


34. Fontao Rodríguez FE. 3 cases of sedation and analgesia using propofol and remifentanil for labor. Rev Esp Anestesiol Reanim 2003;50:418-422.

