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Original contribution

Remifentanil as an alternative to epidural analgesia for vaginal delivery: A meta-analysis of randomized trials

Myeongjong Lee, MD [a], Fang Zhu, MD, PhD [b], Jessica Moodie, MLIS [b], Zhe Zhang, MD [e], Davy Cheng, MD, MSc [b,c], Janet Martin, PharmD, MSc(HTA) [b,c,d,*]

[a] Konkuk University, School of Medicine, Department of Anesthesiology and Pain Medicine, Chungju, South Korea
[b] Centre for Medical Evidence, Decision Integrity and Clinical Impact (MEDICI), University of Western Ontario, London, ON, Canada
[c] Department of Anesthesia & Perioperative Medicine, University of Western Ontario, London, ON, Canada
[d] Department of Epidemiology & Biostatistics, University of Western Ontario, London, ON, Canada
[e] Department of Anesthesiology, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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ABSTRACT

Objectives: Although epidural analgesia is considered the gold standard for labor pain management, its use may be restricted in some conditions due to clinical contraindications or availability, and suitable alternatives may be required. The objective of this meta-analysis was to determine whether evidence from randomized trials suggests remifentanil PCA (R-PCA) results in significant differences in maternal satisfaction, analgesic efficacy, and safety compared with conventional epidural analgesia (EA).
Design: We conducted a meta-analysis after systematically searching MEDLINE, EMBASE and Cochrane Library for all randomized controlled trials (RCTs) allocating parturients to R-PCA or EA and reporting at least one outcome of interest.
Patients: Eight randomized trials of R-PCA vs EA with 2351 patients were included.
Measurements: The primary outcome of interest was maternal satisfaction. Secondary outcomes included visual analog pain score (VAS at 1, 2, 3 h postoperatively), nausea, vomiting, pruritus, hypoxemia, acute respiratory depression or death (maternal or neonatal), need for Cesarean section, and neonatal Apgar score.
Main results: Meta-analysis of the randomized trials showed no significant differences between the R-PCA and EA groups for maternal satisfaction, VAS at 2 or 3 h, nausea, vomiting, need for cesarean section, respiratory depression, umbilical pH, and neonatal Apgar score at 1 min and 5 min. However, incidence of hypoxemia was higher [OR 7.48, 95%CI 3.42–16.36] and VAS at 1 h was slightly higher [WMD 1.33, 95%CI 0.30–2.36] with R-PCA versus EA. Pruritus was less frequent in the R-PCA group [OR 0.54, 95%CI 0.32–0.89]. Acute respiratory failure and death were not reported in any of the studies.
Conclusions: While no significant differences were detected for maternal satisfaction or for most clinical outcomes, this meta-analysis remains underpowered to rule out clinically-important differences due to the few existing randomized trials. For obstetric patients who are not candidates for EA, R-PCA may provide an alternative for analgesia in the peri-partum period, but caution is warranted particularly regarding hypoxemia, and suggests the need for increased surveillance and monitoring for R-PCA. Further adequately powered randomized trials with a focus on clinically-relevant maternal and neonatal outcomes are required to more accurately characterize the relative benefits and risks of R-PCA versus EA in this population.

1. Introduction

Epidural analgesia (EA) remains the 'gold standard' for labor pain relief. However, absolute or relative contraindications exist for EA including spinal abnormalities, hemodynamic instability, bleeding diathesis, suspected infection, allergy to local anesthetics, and patient refusal. For these reasons, alternatives to epidural analgesia are required. Remifentanil is a selective opioid μ-receptor agonist with a rapid onset of action within approximately 1 min and a short context-sensitive half-life of approximately 3 min [1–2]. Its rapid metabolism by non-specific esterases allows for rapid offset after discontinuation of infusion [3]. While it rapidly crosses the placenta, it is generally metabolized and redistributed quickly by the fetus due to non-specific esterase

* Corresponding author at: Centre for Medical Evidence, Decision Integrity and Clinical Impact (MEDICI), Western University, London, Room B3-412, 339 Windermere Road, ON, N6A 5A5, Canada.
E-mail address: Janet.Martin@lhsc.on.ca (J. Martin).

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activity [4]. For these reasons, remifentanil has been proposed as an ideal systemic opioid for labor analgesia. Pre-existing meta-analyses on this topic have not been updated with more recent randomized studies, and none of them focused on maternal satisfaction and all other clinically-relevant maternal and neonatal outcomes for remifentanil-patient controlled analgesia (R-PCA) versus epidural analgesia (EA).

The objective of this meta-analysis of randomized controlled trials (RCTs) was to determine whether remifentanil PCA (R-PCA) provides similar maternal satisfaction, analgesic efficacy, and safety compared with conventional epidural analgesia (EA).

2. Methods

This study was undertaken and reported in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement [5], and with similar methodology as previously described [6].

2.1. Search strategy

MEDLINE, EMBASE, and Cochrane Library were searched up to February 1, 2017, using the MeSH terms "Analgesia, Epidural/", "Analgesia, Obstetrical/", "Labor Pain/" combined with the key words "remifentanil", "epidural analgesia", "obstetric analgesia", and "labor pain". No limitations were placed on language, publication date, or article type.

2.2. Inclusion and exclusion criteria

Inclusion criteria were determined a priori. Published randomized controlled trials of healthy term parturients randomized to remifentanil PCA versus epidural analgesia (using any opioid analgesia or combination) for labor pain control were included. Reviews, conference abstracts (unpublished studies), letters, editorials, and case reports were excluded.

2.3. Data extraction and quality assessment

Two authors (M.L., F.Z.) independently screened trials for potential inclusion, reviewed the full text articles for final inclusion, and performed data extraction using a standardized collection form. Discrepancies were resolved by consensus. Information on patient population, trial design, drug administration (dose, route, and duration), clinical outcomes, and side effects were extracted. Two authors independently assessed study quality using the Jadad scale (0 to 5) for validity assessment (random allocation 0–2, blinding 0–2, and description of withdrawal and dropouts 0–1) [7].

The primary outcome of interest was patient satisfaction, whereby the author's definition of patient satisfaction was used. Since we anticipated that there would be different methods to measure satisfaction, we included all of them qualitatively in a systematic review table, and combined them statistically when appropriate. When scales were used, we converted them to ensure 'improved' satisfaction was indicated by a higher score. We used standardized mean differences to aggregate the scales across studies. Secondary outcomes of interest included: postoperative pain, measured using the Visual Analog Scale (VAS) at 1, 2 and 3 h, or longer; need for cesarean delivery; incidence of maternal side effects (hypoxemia, nausea, vomiting, itching, acute respiratory failure, death); and neonatal outcomes (Apgar score 1, 5 min, neonatal umbilical artery pH, hypoxemia, acute respiratory failure, death). When possible, we preferentially used a desaturation of 94% to indicate hypoxemia. If data was not provided for this definition, we used the next closest desaturation for hypoxemia.

When pain intensity was reported on a 0–100 mm VAS, the data were translated to a 0–10 cm scale. When continuous data were presented as medians and interquartile ranges, means and standard deviations (SDs) were estimated according to the procedures described in the

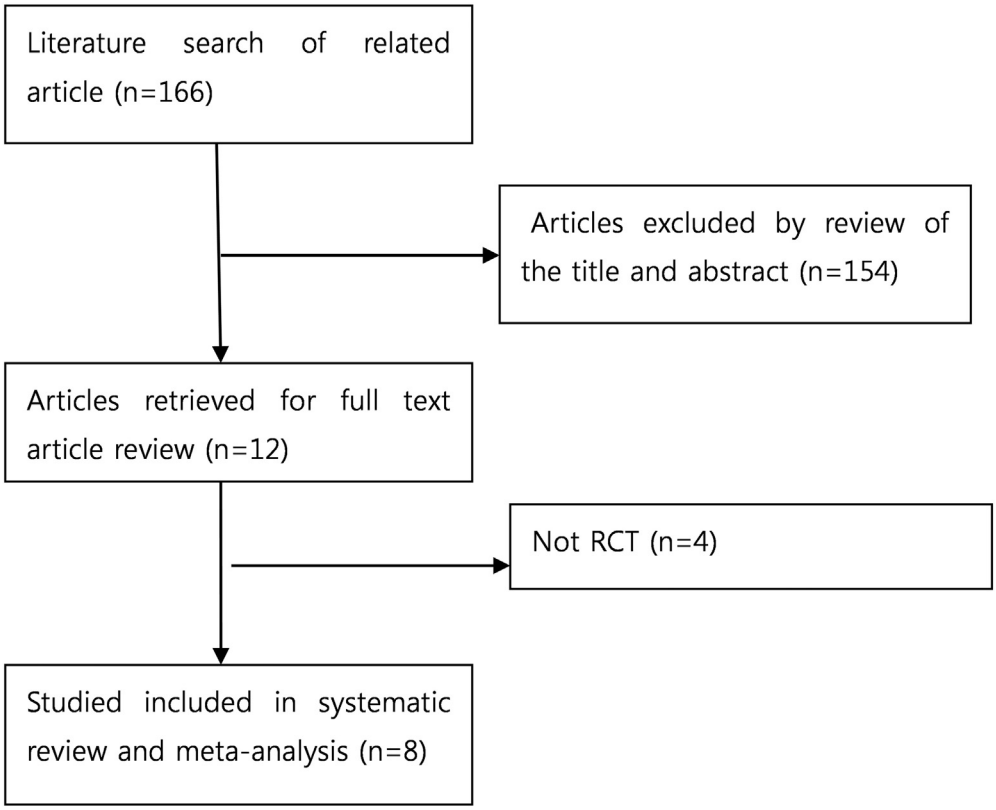

Fig. 1. Flow chart of included studies. PRISMA flow diagram for inclusion and exclusion of studies for evidence reviews.