Continuous intravenous infusion of remifentanil improves the experience of parturient undergoing repeat cesarean section under epidural anesthesia

Wei Yan
Zhejiang University  https://orcid.org/0000-0003-0139-2539

Yun Xiong
Zhejiang University

Yu Yao
Zhejiang University

Feng-jiang Zhang
Zhejiang University

Li-an Yu
Zhejiang University

Min Yan (✉️ zryanmin@zju.edu.cn)
Zhejiang University  https://orcid.org/0000-0002-1355-1261

Research Article

Keywords: Remifentanil; Epidural anesthesia; Repeat cesarean delivery

Posted Date: January 30th, 2019

DOI: https://doi.org/10.21203/rs.2.255/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License

Version of Record: A version of this preprint was published on December 30th, 2019. See the published version at https://doi.org/10.1186/s12871-019-0900-x.
Abstract

**Background**: To observe the effects of intravenous remifentanil on maternal comfort, maternal and neonatal safety during repeat cesarean section under epidural anesthesia.

**Methods**: A total of 80 parturient undergoing repeat cesarean section were involved in the study. The patients were randomly divided into the intravenous remifentanil-assisted epidural group (group R) and epidural group (group E), respectively (n=40). In group R, the remifentanil was continuously intravenously infused as an adjuvant to epidural anesthesia. In group E, 0.75% ropivacaine epidural or intravenous ketamine was administered as needed. Parturient baseline characteristics, vital signs, VAS scores, and comfort scores during surgery were recorded. Adverse effects were also recorded.

**Results**: A total of 80 patients were enrolled in the current study and the final analyses included 39 patients in group R and 38 patients in group E. No differences in patients' baseline characteristics were found between the two groups (p > 0.05). Compared with group E, the comfort score was significantly higher in group R (9.1±1.0 vs. 7.5±1.3, p<0.001), whereas the maximum VAS score was significantly lower in group R (1.8±1.2 vs. 4.0±0.9, p<0.001). Maternal and neonatal adverse effects did not differ between the two groups during surgery (p>0.05).

**Conclusions**: Continuous intravenous infusion of low-dose remifentanil can significantly improve the experience of parturients undergoing repeat cesarean section under epidural anesthesia, without obvious maternal or neonatal adverse effects.

**Keywords**: Remifentanil; Epidural anesthesia; Repeat cesarean delivery

**Background**

Epidural anesthesia is a popular and safe anesthetic technique for cesarean section\(^{[1,2]}\), which has few maternal and neonatal adverse effects, as well as good controllability. However, unsatisfactory analgesia frequently occurs, particularly regarding visceral pain caused by visceral traction during cesarean section\(^{[3,4]}\). Additionally, when the anxiety regarding surgery is included, epidural anesthesia is not a good experience for parturients.

In China, with the implementation of the second child policy, the number of parturients with a scarred uterus has greatly increased; this event leads to an increased number of intra-abdominal adhesions\(^{[5]}\). Parturients with a scarred uterus may experience longer surgery duration and greater intensity of peritoneal traction, compared with uniparous women\(^{[3]}\), which results in more serious intraoperative visceral pain during cesarean section. Propofol, thiopentone, and ketamine have been administered intravenously as rescue analgesia during cesarean section; however, these may reduce the umbilical arterial pO\(_2\) and Apgar score of neonates\(^{[6,7]}\).
Many studies have shown that remifentanil has almost no adverse neonatal or maternal effects during cesarean section; thus, they have suggested its use as a replacement for standard opioids in cesarean section\cite{8-10}. In our clinic, we found that continuous intravenous infusion of low-dose remifentanil has a good rescue analgesic effect on incomplete epidural analgesia and provides a degree of sedation during cesarean section, which improves the patient experience. Thus, we designed this prospective, randomized, controlled study to investigate the effects of continuous intravenous infusion of remifentanil 0.05 $\mu$g·kg$^{-1}$·min$^{-1}$ on parturient experience and neonatal safety among patients undergoing epidural anesthesia during repeat cesarean section.

**Methods**

**Ethics**

The study was approved by the ethics committee of Huzhou Maternity & Child Care Hospital (Ethical Committee number 201801; Chairperson Ping-ya He) and written informed consent was provided by all patients prior to enrollment in the study.

**Study design and patient population**

A total of 80 patients with repeat cesarean section, aged 23-36 years (weight 56-90 kg, American Society of Anesthesiologists levels I and II) were involved in the study. The patients were randomly placed in either the intravenous remifentanil-assisted epidural group (group R) or the epidural group (group E).

**Criteria for inclusion and exclusion**

Patients undergoing repeat cesarean section, with full-term, singleton pregnancies, who had arranged for epidural anesthesia, were included in this study. Patients with contraindications for epidural anesthesia, history of allergy to bupivacaine or opioids, history of spinal surgery, or intrauterine hypoxia were excluded from this study. Patients with epidural anesthesia puncture failure, poor effect of epidural anesthesia, or intraoperative hemorrhage were also excluded from the analysis.

**Preoperative preparations and anesthesia protocol**

All patients fasted for 6 h and discontinued fluid intake 2 h before repeat cesarean section. Intravenous access was established, 5 L/min oxygen was administered, and Ringer’s lactate 8 ml/kg was preloaded after patients entered the operating room. Electrocardiography, noninvasive arterial pressure, respiratory rate, and pulse oximetry were routinely monitored for all parturients.

Before epidural anesthesia was administered, patients were placed in the left lateral decubitus position. The epidural space was cannulated at the L2-3 interspace with the midline approach, using an 18-gauge Tuohy needle. A loss-of-resistance to the saline technique was used to affirm the puncture; then, a 20-gauge epidural catheter was advanced 3 cm cephalad. Three milliliters 1.5% lidocaine with 10 $\mu$g adrenaline was injected through the epidural catheter as a test dose. Epidural administration of 0.75%
ropivacaine was performed in two groups until the epidural anesthesia level of all parturients reached T6. In group R, remifentanil was continuously intravenously infused at a rate of 0.05 μg·kg\(^{-1}\)·min\(^{-1}\) at the beginning of the operation. The intravenous infusion rate of remifentanil was increased by 0.025 μg·kg\(^{-1}\)·min\(^{-1}\) if patients complained of discomfort or pain. The maximum speed of intravenous infusion did not exceed 0.15 μg·kg\(^{-1}\)·min\(^{-1}\). If excessive sedation or respiratory depression occurred, intravenous infusion of remifentanil was reduced 0.025 μg·kg\(^{-1}\)·min\(^{-1}\) until infusion was completely discontinued. In group E, if the patients complained of discomfort or pain, 0.75% epidural ropivacaine was administered as needed. Intravenous infusion of ketamine was administered as needed, or general anesthesia was performed if the discomfort or pain were not relieved.

If the saturation of pulse oxygen (SpO\(_2\)) was <95% or respiratory rate (RR) was <8 times/min (i.e., respiratory depression was observed), the parturient was awakened and oxygen was administered with a pressure mask. If the heart rate (HR) was <50 beats/min, intravenous atropine 0.5 mg was administered. If hypotension (a systolic blood pressure (SBP) reduction of >30% or a value of <90 mmHg) occurred, intravenous ephedrine 5-10 mg was administered. All anesthesia procedures were performed by the same senior anesthesiologist and all data were recorded by an anesthesia nurse. Patients in both groups were excluded from this study if the anesthetic block level did not reach T10, or if they were changed to general anesthesia 15 min after epidural administration.

**Measurements**

The following parturient data were recorded: age, body mass index (BMI), weight, ASA status, dose of ropivacaine, gestational weeks, dose of remifentanil, and epidural anesthesia block level (counted from the sacral vertebra\(^{[11]}\)) were recorded. SpO\(_2\), mean arterial pressure (MAP), HR, and RR were recorded before anesthesia (T\(_0\)), as well as at skin incision (T\(_1\)), delivery of baby (T\(_2\)), uterine suture (T\(_3\)), and intraoperative traction (T\(_4\)) in all parturients. The visual analogue scale (VAS) score was recorded at T\(_1\), T\(_2\), T\(_3\), and T\(_4\); the maximum VAS score during surgery was also recorded. The degree of comfort during surgery was assessed using the numerical rating scale (NRS, 0 = least comfort imaginable, 10 = very comfortable). The use of intraoperative oxytocin was recorded in both groups. Incidences of intraoperative respiratory depression (RR<8 times/min), bradycardia, hypotension, and postoperative adverse reactions were recorded for both groups; Apgar scores were recorded at 1and 5 min after birth for both groups, as were the numbers of neonatal resuscitations and the pH value of neonatal umbilical arterial blood.

The comfort scores during surgery was the primary outcome measure of the study; the secondary outcomes were the maximum VAS score, and maternal and newborn adverse effects during surgery.

**Statistical analysis**

In a preliminary trial of 20 patients, the comfort scores during surgery were 8.9±0.9 and 7.8±1.6 in groups R and E, respectively. Based on the preliminary trial, 26 patients were required per group to detect a 15%
increase of comfort score for 90% power and an α level of 0.05, with a drop-out rate of 15%. Data are expressed as mean ± standard deviation (SD), or numbers of patients, as appropriate. Statistical analyses were performed using independent t-tests, the chi-squared test, Fisher’s exact test, and repeated measures analysis of variance, as appropriate. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). \( p < 0.05 \) was considered to indicate statistical significance.

**Results**

A total of 80 patients were enrolled in the current study, and three patients were excluded from data analysis because they were changed to general anesthesia. Thus, the final analyses included 39 patients in group R and 38 patients in group E (Fig. 1). No differences were found in the patients’ baseline characteristics between the two groups (\( p > 0.05 \)) (Table 1).

There were no differences in anesthesia spread levels before surgery and at the end of surgery between the two groups (both \( p > 0.05 \)). Compared with group R, the ropivacaine dosage was significantly increased in group E (\( p < 0.001 \)); the usage of remifentanil in group R was 169±14.2 μg; and the numbers of patients with ketamine administration and repeat oxytocin administration did not differ between the two groups (both \( p > 0.05 \)) (Table 2).

Compared with group E, the comfort score was significantly higher in parturients in group R (9.1±1.0 vs. 7.5±1.3, \( p < 0.001 \)), whereas the maximum VAS score was significantly lower in parturients in group R (1.8±1.2 vs. 4.1±1.0, \( p < 0.001 \)) (Fig 2 and 3). Compared with group E, the VAS score was significantly lower in group R at \( T_1 \) to \( T_4 \) (all \( p < 0.001 \)), Fig 4. Compared with group E, the incidence of VAS scores \( \geq 4 \) was clearly reduced in group R (65.8% vs. 12.8%, \( p < 0.001 \)).

There were no significant differences in MAP, HR, or RR between the two groups at \( T_0 \) to \( T_5 \) (all \( p > 0.05 \)) (Fig 5-7). Adverse reactions did not differ between the two groups during surgery (all \( p > 0.05 \)) (Table 3). The number of neonatal resuscitations, pH value of neonatal umbilical arterial blood, and Apgar scores at 1 and 5 min after birth were not different between the two groups (all \( p > 0.05 \)) (Table 4).

**Discussion**

The primary finding of this study was that intravenous infusion of remifentanil can significantly improve the experience of parturients undergoing epidural anesthesia during repeat cesarean section. Visceral pain was relieved during surgery without obvious maternal or neonatal adverse effects.

Previous studies have shown that the incidence rate of visceral pain ranged from 10% to 50% in parturients undergoing epidural anesthesia\[^4,12\]. In the current study, approximately 67.5% parturients experienced obvious visceral pain during surgery without remifentanil, which was an obvious increase compared with the rate in previous studies because the subjects were undergoing repeat cesarean
section. Indeed, even if the sensory block plane reaches T4, many maternal complaints remain regarding unpleasant feelings related to visceral traction\cite{13}. This maybe because visceral pain is primarily transmitted through unmyelinated C fibers; although the level of sensory block in epidural anesthesia reaches T4, C fibers are not completely blocked. Opioids can inhibit C fibers, in addition to their central analgesic effects\cite{14}. Thus, the parturient who received remifentanil experienced lower visceral pain, such that their comfort scores increased.

A previous study showed that 0.1 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) remifentanil can provide effective analgesia during local anesthesia with little influence on respiration and hemodynamics in a general patient population\cite{15}. In the current study, 0.05 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) remifentanil was administered; we also found that it showed little influence on respiration and hemodynamics in parturients. Notably, parturients with epidural anesthesia alone may experienced greater hypotension because larger doses of ropivacaine were used. Avramov et al.\cite{15} and Kan et al.\cite{8} reported that remifentanil can also provide a degree of sedation, which improved patient comfort levels in the current study. In obstetric surgery, it is important to determine whether administered drugs affect uterine contractions. The present study showed that intravenously administered low-dose remifentanil had a minimal effect on uterine contraction, based on the requirement for repeated usage of oxytocin and the blood loss during surgery.

Kan et al.\cite{8} reported that remifentanil can cross the placenta, and that it appears to be rapidly metabolized, redistributed, or both, without neonatal adverse effects. Lee et al.\cite{10} also found that remifentanil can be safely used for vaginal delivery. In the present study, as reported in previous studies, no neonatal adverse effects were observed, including changes in rates of neonatal resuscitation, pH value of neonatal umbilical arterial blood, and Apgar scores. Van de Velde et al.\cite{16} reported that a 0.50 \(\mu\text{g} / \text{kg}\) intravenous bolus of remifentanil induction dose, followed by a continuous infusion of 0.20 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), caused partial neonatal depression and required brief mask-assisted ventilation. Noskova et al.\cite{17} reported that a bolus of 1 \(\mu\text{g} / \text{kg}\) remifentanil prior to induction of general anesthesia decreased Apgar scores at 1 min after cesarean delivery, although the clinical symptoms were short. These observations were not found in current study, because the dosage of remifentanil injection was lower than in the prior studies\cite{16, 17}. Thus, low dosage of remifentanil is recommended for parturients during cesarean section.

The current study has some limitations. First, previous studies have shown that epidural opioid administration may relieve visceral pain under epidural anesthesia in parturients\cite{3, 18}, but we did not compare the effects of intravenous remifentanil and epidural opioid on visceral pain relief. Second, only 0.05 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) remifentanil was used in the current study; whether this is the optimum dose requires further study.

The present study demonstrated that, in parturients undergoing repeat cesarean section, intravenous continuous infusion of low-dose remifentanil can significantly enhance the parturient experience during epidural anesthesia, without obvious maternal or neonatal adverse effects.
Abbreviations

VAS: Visual analogue scale
BMI: Body mass index
ASA: American Society of Anesthesiologists
HR: Heart rate
RR: Respiratory rate
SBP: Systolic blood pressure
MAP: Mean arterial pressure
SpO₂: Saturation of pulse oxygen

Declarations

Registration

This study was pre-registered at

http://www.chictr.org.cn/index.aspx (ChiCRT1800018423)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

- Wei Yan
  Role: This author helped to conduct the study and write the manuscript.
- Yun Xiong
  Role: This author helped to conduct the study.
- Feng-jiang Zhang
  Role: This author helped to conduct the study.
- Li-na Yu
  Role: This author helped to analyze the data.
Min Yan

Role: This author helped to design the study and revise the manuscript.

Acknowledgements

We would like to thank Qing-he Zhou for their assistance in the collection with the study. This work was supported by Huzhou Maternity & Child Care Hospital.

References

1. Setayesh AR, Kholdebarin AR, Moghadam MS, Setayesh HR. The Trendelenburg position increases the spread and accelerates the onset of epidural anesthesia for Cesarean section. Can J Anaesth. 2001,48(9):890-3.

2. Davies SJ, Paech MJ, Welch H, Evans SF, Pavy TJ. Maternal experience during epidural or combined spinal-epidural anesthesia for cesarean section: a prospective, randomized trial. Anesth Analg. 1997,85(3):607-13.

3. Lu Q, Dong CS, Yu JM, Sun H, Sun P, Ma X, et al. The dose response of sufentanil as an adjuvant to ropivacaine incesarean section for relief from somato-visceral pain under epidural anesthesia in parturients with scarred uterus. Medicine (Baltimore). 2018,97(38):e12404.

4. Alahuhta S, Kangas-Saarela T, Hollmén Al, Edström HH. Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. Acta Anaesthesiol Scand. 1990,34(2):95-8.

5. Salim R, Kadan Y, Nachum Z, Edelstein S, Shalev E. Abdominal scar characteristics as a predictor of intra-abdominal adhesions at repeat cesarean delivery. Fertil Steril. 2008,90(6):2324-7.

6. Houthoff Khemlani K, Weibel S, Kranke P, Schreiber JU. Hypnotic agents for induction of general anesthesia in cesarean section patients: A systematic review and meta-analysis of randomized controlled trials. J Clin Anesth. 2018,48:73-80.

7. Heesen M, Böhmer J, Brinck EC, Kontinen VK, Klöhr S, Rossaint R, et al. Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. Acta Anaesthesiol Scand. 2015,59(4):414-26.

8. Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology. 1998,88(6):1467-74.

9. Noskova P, Blaha J,Bakhouche H, Kubatova J, Ulrichova J, Marusicova P, et al. Neonatal effect of remifentanil in general anaesthesia for caesarean section: a randomized trial. BMC Anesthesiol. 2015,26;15:38.

10. Lee M, Zhu F, Moodie J, Zhang Z, Cheng D, Martin J. Remifentanil as an alternative to epidural analgesia for vaginal delivery: A meta-analysis of randomized trials. J Clin Anesth. 2017, 39:57-63.

11. Zhou QH, Xiao WP, Shen YY. Abdominal girth, vertebral column length, and spread of spinal anesthesia in 30 minutes after plain bupivacaine 5 mg/mL. Anesth Analg. 2014,119(1):203-6.
12. Crawford JS, Davies P, Lewis M. Some aspects of epidural block provided for elective caesarean section. Anaesthesia. 1986,41(10):1039-46.

13. Ousley R, Egan C, Dowling K, et al. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. Anaesthesia. 2012,67(12):1356-63.

14. Ma D, Sapsed-Byrne SM, Chakrabarti MK, Ridout D, Whitwam JG. Synergism between sevoflurane and intravenous fentanyl on A delta and C somatosympathetic reflexes in dogs. Anesth Analg. 1998,87(1):211-6.

15. Avramov MN, Smith I, White PF. Interactions between midazolam and remifentanil during monitored anesthesia care. Anesthesiology. 1996;85(6):1283-9.

16. Van de Velde M, Teunkens A, Kuypers M, Dewinter T, Vandermeersch E. General anaesthesia with target controlled infusion of propofol for planned caesarean section: maternal and neonatal effects of a remifentanil-based technique. Int J Obstet Anesth. 2004,13(3):153-8.

17. Noskova P, Blaha J, Bakhouche H, Kubatova J, Ulrichova J, Marusicova P, et al. Neonatal effect of remifentanil in general anaesthesia for caesarean section: a randomized trial. BMC Anesthesiol. 2015,26;15:38.

18. Parpaglioni R, Baldassini B, Barbati G, Celleno D. Adding sufentanil to levobupivacaine or ropivacaine intrathecal anaesthesia affects the minimum local anaesthetic dose required. Acta Anaesthesiol Scand. 2009,53(9):1214-20.

Tables

Table 1 - Comparison of parturients' baseline characteristics

|                          | Group R (n=39) | Group E (n=38) | P value |
|--------------------------|----------------|----------------|---------|
| Age, years               | 30.8±3.4       | 30.3±2.6       | 0.541   |
| BMI, kg/m²               | 26.7±2.2       | 27.4±2.0       | 0.185   |
| ASA, I/II                | 37/2           | 36/2           | 1.000   |
| Pregnancy time, weeks    | 38.9±0.8       | 38.9±0.9       | 0.849   |
| Surgery duration, min     | 41.7±10.6      | 46.2±13.9      | 0.111   |

Data are expressed as mean ± standard deviation, unless otherwise indicated.

BMI = body mass index, ASA = American Society of Anesthesiologists.
Table 2 - Information regarding intraoperative anesthetic drugs and oxytocin usage

|                          | Group R (n=39) | Group E (n=38) | Pvalue |
|--------------------------|---------------|---------------|--------|
| Anesthesia level, segment|               |               |        |
| Before surgery           | 17.1±0.4      | 17.2±0.5      | 0.572  |
| At the end of the surgery| 15.9±0.4      | 16.1±0.5      | 0.161  |
| Ropivacaine dosage, ml   | 16.8±0.4*     | 18.0±1.4      | <0.001 |
| Remifentanil dosage, μg  | 169.2±14.2    | 0             | <0.001 |
| Ketamine, n              | 1             | 4             | 0.340  |
| Repeat oxytocin admin., n| 6             | 7             | 0.959  |
| Blood loss during surgery, ml | 308±62      | 311±109       | 0.888  |

Data are expressed as mean ± standard deviation or n.

*Statistically significant difference between groups according to independent-sample Student's t-tests

Table 3 - Information regarding adverse reactions

|                          | Group R (n=39) | Group E (n=38) | Pvalue |
|--------------------------|---------------|---------------|--------|
| Bradycardia, n           | 1             | 0             | 1.000  |
| Hypotension, n           | 0             | 4             | 0.117  |
| Respiratory depression, n| 2             | 0             | 0.485  |
| Nausea and vomiting, n   | 1             | 5             | 0.191  |

Data are expressed as n.

Table 4 - Neonatal-related information after delivery
|                              | Group R (n=39) | Group E (n=38) | P value |
|------------------------------|---------------|----------------|--------|
| Neonatal resuscitation, n    | 2             | 2              | 1.000  |
| pH value of umbilical arterial blood | 7.376±0.024   | 7.380±0.023    | 0.481  |
| Apgar score                  |               |                |        |
| 1 min                        | 9.72±0.60     | 9.58±0.64      | 0.331  |
| 5 min                        | 9.92±0.27     | 9.92±0.27      | 0.974  |

Data are expressed as mean ± standard deviation or n.

PH = pondus hydrogenii.

**Figures**
Figure 1

Consort flow diagram.
Figure 2

Comparison of comfort score between the two groups. Compared with group E, the comfort score was significantly higher in group R (9.1±1.0 vs. 7.5±1.3, p<0.001).
Comparison of maximum visual analogue scale (VAS) score between the two groups. Compared with group E, the maximum VAS score was significantly lower in group R (1.8±1.2 vs. 4.0±0.9, p<0.001).

Figure 3
Comparison of visual analogue scale (VAS) score between the two groups at T1 to T4. Compared with group E, the VAS score was significantly lower in group R at T1-T4 (all p<0.001). T1: skin incision; T2: delivery of baby; T3: uterine suture; T4: intraoperative traction.
Figure 5

Comparison of mean arterial pressure (MAP) between the two groups at T0 to T4. There was no significant difference in MAP between the two groups at T0 to T4 (all p>0.05). T0: before anesthesia; T1: skin incision; T2: delivery of baby; T3: uterine suture; T4: intraoperative traction.
Figure 6

Comparison of heart rate (HR) between the two groups at T0 to T4. There was no significant difference in HR between the two groups at T0 to T4 (all p>0.05). T0: before anesthesia; T1: skin incision; T2: delivery of baby; T3: uterine suture; T4: intraoperative traction.
Figure 7

Comparison of respiratory rate (RR) between the two groups at T0 to T4. There was no significant difference in RR between the two groups at T0 to T4 (all p>0.05). T0: before anesthesia; T1: skin incision; T2: delivery of baby; T3: uterine suture; T4: intraoperative traction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc