Efficacy and safety of remifentanil for analgesia in cesarean delivery

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Abstract
Background: This study aimed to assess the efficacy and safety of remifentanil as a general anesthetic during cesarean delivery.

Material and Methods: Fifty women with singleton pregnancies undergoing cesarean delivery were randomly divided into intervention and control groups, each group containing 25 subjects. Participants in the intervention group received remifentanil (infused at 2 μg/kg/h), whereas subjects in the control group were given dexmedetomidine (infused at 0.4 μg/kg/h). Outcome measurements included mean arterial blood pressure (MAP), heart rate (HR), bispectral index (BIS), Apgar scores at 1 and 5 minutes, and the pH, PCO₂, PO₂, and base excess (BE) of umbilical venous and arterial blood.

Results: Forty-four participants completed the study. Patients in the intervention group did not experience greater effect and safety than those in the control group (P > .05), although MAP and BIS values decreased significantly immediately before laryngoscopy (P < .05). In addition, BIS values were reduced significantly at the time of skin incision, at uterine incision, and immediately after fetal delivery when compared with baseline values in both groups (P < .01).

Conclusion: This study concluded that remifentanil and dexmedetomidine exhibited similar efficacy and safety during general anesthesia for cesarean delivery.

Keywords: cesarean delivery, dexmedetomidine, pregnancy, randomized controlled trial, remifentanil

1. Introduction

Opioids are commonly used for the cesarean section (CS). However, previous studies reported that they can cause respiratory depression in the neonates. Thus, they are usually avoided during the induction of general anesthesia for CS.

On the contrary, it is also reported that insufficient depth of analgesia in parturients is an issue for obstetric anesthetists during fetal delivery. The opioid remifentanil has been recommended as an attractive alternative anesthetic in parturients undergoing CS delivery. It is an ultrashort-acting μ1-receptor agonist with a half-time of 3 to 10 minutes, and can rapidly cross the placenta. However, it can also be eliminated from fetal circulation at the time of delivery. It is often be used for external cephalic version intervention, surgery, and propofol injection.

Dexmedetomidine is an alternative anesthetic for women undergoing CS. It is a highly selective α2-adrenoceptor agonist, and can be used for sedation, analgesia, and amnesia induction without depressing respiratory function. Its successful use in CS has been reported in patients with contraindications to neuraxial anesthesia, as well as in those refusing neuraxial anesthesia. Additionally, dexmedetomidine has been used as an adjunctive anesthetic with opioid-based analgesia if pain relief was not satisfactory with the latter alone. It is also reported that it was successfully used for CS delivery in pregnant women with spinal muscular atrophy and Klippel-Feil syndrome, and also for other surgeries.

In this study, we tested the hypothesis that remifentanil and dexmedetomidine had similar efficacy in blunting hemodynamic responses to intubation and safeguarding neonates in Chinese pregnant women undergoing CS delivery.

2. Material and methods

This study was designed as a randomized controlled trial. Fifty parturients with singleton pregnancies at term or near term for elective CS were included. The study was conducted at The Affiliated Hongqi Hospital of Mudanjiang Medical University from January 2014 to December 2016. The trial was approved by the Medical Ethical Committee of The Affiliated Hongqi Hospital of Mudanjiang Medical University. The authors report no conflicts of interest.

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jiang Medical University. All participants met the inclusion/exclusion criteria, and were randomly divided and allocated to the intervention group (treated with remifentanil) or control group (treated with dexmedetomidine) in a 1:1 allocation ratio.

The inclusion criteria stipulated that participants should fall into the American Society of Anesthesiologists (ASA) physical status I or II grades, with a singleton at term (≥38 weeks). All subjects had contraindications to regional anesthesia. The subjects were excluded if they had active labor, preeclampsia, multiple pregnancy, previous uterine surgery, neurological disease, maternal cardiovascular disease, severe hypertension, allergy to remifentanil or dexmedetomidine, predicted difficult airway management, or fetal abnormalities.

Randomization was conducted using a computerized number generator in SAS 8.3 (SAS Institute, Inc., Cary, NC). After randomization, assignments were concealed and were masked to the outcome assessors and data analysts were blinded to the intervention allocation.

All patients were recruited through the clinic of the obstetrics and gynecology department at The Affiliated Hongqi Hospital, Mudanjiang Medical University. All subjects were randomized to either the intervention or the control group after confirmation of singleton pregnancy using clinical evaluation and ultrasound scan. All investigators were trained to administer the drug before the study. All included subjects were informed about the research and given an information sheet. Consent was obtained from all included pregnant women.

Patients in the intervention group were administered remifentanil (2 μg/kg in the first 10 minutes, followed by a continuous infusion of 2 μg/kg/h for approximately 7 minutes) before the delivery. The participants in the control group received dexmedetomidine (0.4 μg/kg during the first 10 minutes, followed by a continuous infusion of 0.4 μg/kg/h for approximately 7 minutes) before the delivery.

Outcomes were measured by mean arterial blood pressure (MAP), heart rate (HR), bispectral index (BIS), Apgar scores at 1 and 5 minutes, pH, PCO2, PO2, and base excess (BE) of umbilical venous and arterial blood.

2.1. Statistical analysis

The estimated sample size was 21 patients in each group with a 20% variation compared with baseline level, α = 0.05 (2-sided) and β = 0.20. Assuming a 20% dropout rate, at least 50 patients with 25 in each group should have been recruited in this study. All outcome data were analyzed by an intention-to-treat approach. Wilcoxon and t tests were used to analyze the data using relative risks and 95% confidence intervals, respectively.

3. Results

Seventy-one women with singleton pregnancies undergoing cesarean delivery were initially recruited (Fig. 1). Twenty-one participants were excluded because they neither meet the inclusion criteria (n = 18) nor agreed to participate in this study (n = 3). Fifty subjects were included and were randomly divided into intervention and control groups, with 25 patients in each group. Four patients withdrew from the study (Fig. 1). The basic characteristics of all included participants in each group at baseline are shown in Table 1. No significant differences in patient characteristics at baseline were found (Table 1).

No significant differences regarding the MAP, BIS, and HR values were found between the 2 groups (Figs. 2–4). However, when compared with the baseline, MAP decreased significantly immediately before laryngoscopy (P < .05, Fig. 2) in both groups. Moreover, BIS values also decreased significantly immediately before laryngoscopy, at skin incision, at uterine incision, and immediately after fetal delivery, when compared with those at baseline in both groups (P < .01, Fig. 3). However, no significant difference in HR was recorded immediately before laryngoscopy, at skin incision, at uterine incision, or immediately after fetal delivery, compared to that at baseline (P > .05, Fig. 4).

The secondary outcome measurements are shown in Table 2. There are not significant differences in Agar score at 1 and 5 minutes, pH, PCO2, PO2, and BE of umbilical venous and arterial blood after treatment between the 2 groups (P > .05, Table 2). In addition, no treatment-related deaths occurred in either group.
4. Discussion

Previous studies have reported that remifentanil has a positive effect on general anesthesia during cesarean delivery in both healthy pregnant patients \[8\] and severe preeclamptics. \[29–31\] However, the other study found negative effects in healthy parturients when using remifentanil at a dose of 0.5 mg/kg, followed by an infusion of 0.15 mg/kg/min until peritoneal incision.\[32\] Additionally, another study was designed to assess the effects of remifentanil and dexmedetomidine for CS.\[33\] It found that both remifentanil and dexmedetomidine are effective for CS.\[33\] However, remifentanil has potential risk of neonatal transient respiratory depression.\[33\] Our study is consistent with the previous study.\[33\] In our study, remifentanil was infused at a dose of 2 mg/kg in the first 10 minutes, followed by a continuous infusion of 2 mg/kg/h for approximately 7 minutes before fetal delivery.

Dexmedetomidine has also been shown to be useful for general anesthesia during cesarean delivery in healthy parturients.\[28\] It has been reported that the administration of dexmedetomidine at 0.4 and 0.6 mg/kg/h during 20 minutes was effective in preoperative patients.\[12\] In this study, dexmedetomidine was infused at a dose of 2 μg/kg in the first 10 minutes, followed by a continuous infusion of 2 μg/kg/h for approximately 7 minutes before fetal delivery. In this study, no significant differences in any of the outcome measurements were found between the 2 groups. Fortunately, MAP and BIS values decreased significantly immediately before laryngoscopy; BIS alone also reduced significantly at the time of skin incision, at uterine incision, and immediately after fetal delivery when compared with baseline in both groups.

This study had several limitations. First, this study had a small sample size, which may affect the results. Second, this study was conducted at The Affiliated Hongqi Hospital of Mudanjiang Medical University; most participants were of Han ethnicity, with only 5 of Korean ethnicity, which may affect the generalizability of this finding to other hospitals and other ethnicities. Third, the patients also received other interventions.

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**Table 1**

| Characteristics                          | Intervention group (n = 25) | Control group (n = 25) | P   |
|------------------------------------------|-----------------------------|------------------------|-----|
| Age, y                                   | 32.8 (3.3)                  | 34.4 (4.1)             | .13 |
| Body mass index, kg/m²                   | 27.2 (3.0)                  | 27.6 (3.2)             | .73 |
| Race                                     |                             |                        |     |
| Korean ethnicity                         | 3 (12.0)                    | 5 (20.0)               | .44 |
| Han ethnicity                            | 22 (88.0)                   | 20 (80.0)              | .44 |
| Gestation age, wk                        | 38.1 (1.3)                  | 38.4 (0.6)             | .20 |
| Birth weight, g                          | 3083.7 (425.4)              | 3205.7 (433.1)         | .34 |
| General anesthesia reasons               |                             |                        |     |
| Refuse to regional anesthesia            | 14 (56.0)                   | 12 (48.0)              | .57 |
| Thrombocytopenia                         | 5 (20.0)                    | 6 (24.0)               | .73 |
| Previous spinal surgery                  | 2 (8.0)                     | 3 (12.0)               | .64 |
| Skin infection of the lumbar spine       | 2 (8.0)                     | 3 (12.0)               | .64 |
| Aplastic anemia                          | 2 (8.0)                     | 1 (4.0)                | .56 |

Data are presented as mean ± standard deviation or number (%).

**Table 2**

| Outcome measurements                     | Intervention group (n = 25) | Control group (n = 25) | P   |
|------------------------------------------|-----------------------------|------------------------|-----|
| Agar at 1 min                            |                             |                        |     |
| 0–6                                      | 9 (36.0)                    | 7 (28.0)               | .55 |
| 7–10                                     | 16 (64.0)                   | 18 (72.0)              | .55 |
| mean                                     | 7.5 (1.9)                   | 8.0 (1.7)              | .33 |
| Agar at 5 min                            |                             |                        |     |
| 0–6                                      | 0 (0.0)                     | 1 (4.0)                | .49 |
| 7–10                                     | 25 (100.0)                  | 24 (96.0)              | .49 |
| mean                                     | 9.1 (0.9)                   | 8.9 (1.1)              | .48 |
| Umbilical artery                         |                             |                        |     |
| pH                                       | 7.34 (0.03)                 | 7.35 (0.04)            | .32 |
| PCO₂, mmHg                               | 43.1 (4.6)                  | 43.5 (4.9)             | .77 |
| PO₂, mmHg                                | 55.9 (15.0)                 | 57.7 (16.1)            | .68 |
| BE, mmol/L                               | −2.0 (2.0)                  | −1.8 (1.9)             | .72 |
| Umbilical artery                         |                             |                        |     |
| pH                                       | 7.32 (0.04)                 | 7.33 (0.05)            | .43 |
| PCO₂, mmHg                               | 50.1 (5.3)                  | 49.7 (5.8)             | .80 |
| PO₂, mmHg                                | 31.7 (6.0)                  | 33.1 (6.4)             | .42 |
| BE, mmol/L                               | −1.6 (2.1)                  | −1.4 (2.1)             | .88 |

Note: Data are presented as mean ± standard deviation or number (%). BE = base excess, PCO₂ = partial pressure of carbon dioxide, PO₂ = partial pressure of oxygen.
and the observed effects may have been the result of synergism between these other interventions and remifentanil or dexmedetomidine. Finally, although no adverse events were documented at the end of our evaluation, they remain a possibility in the future.

5. Conclusion

This study found that both remifentanil and dexmedetomidine had a positive effect on general anesthesia, and demonstrated similar safety during cesarean delivery. Further studies should focus on a larger sample size to verify this result.

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