

The Efficacy and Safety of Continuous Intravenous Administration of Remifentanyl for Birth Pain Relief: An Open Study of 205 Parturients

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In an observational study, we prospectively evaluated the efficacy and safety of remifentanyl in 205 parturients. Remifentanyl was administered as a continuous infusion. The initial infusion of $0.025 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was increased in a stepwise manner to a maximum dose of $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Maternal pain, other maternal and fetal variables, side effects, and satisfaction were recorded. The mean (\pm SD) visual analog score before the start of the infusion was 9.4 ± 1.2 cm and decreased to 5.1 ± 0.4 cm after 5 min and 3.6 ± 1.5 cm after 30 min. The maternal side effects were minimal and no fetal or neonatal side effects were noted.

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Remifentanyl, an opioid with a strong affinity for μ -opioid receptors, is characterized by short latency (time to peak effect of 60–90 s), low volume of distribution volume in steady state, high clearance (2800 mL/min), low lipid solubility, a pK_a very close to plasma pH (7.1), and a context-sensitive half-life of 3–5 min.¹ Remifentanyl is currently not approved for obstetric use, although its use for the treatment of labor pain has been described in a number of reports.^{2–18}

The purpose of this prospective observational study was to examine the maternal and neonatal safety of a continuous IV infusion of remifentanyl during labor and to evaluate the analgesic effects and patient satisfaction.

METHODS

After obtaining approval by the local ethics committee and written informed consent at 32-wk gestation from the patients, a prospective observational trial was conducted between January 2006 and September 2007. Neuraxial labor analgesia is not available in our birthing center. Only women who specifically requested systemic analgesia were considered eligible to participate in the

study. The inclusion criteria were term singleton pregnancy and ASA physical status I and II patients in active labor with cephalic presentation. Exclusion criteria were allergy or hypersensitivity to remifentanyl or other opioid analgesia during the same labor. Chronic opioid use was not considered an exclusion criterion.

After admission to the labor and delivery room, IV access was established with an 18-G cannula. Remifentanyl was administered at a concentration of $25 \mu\text{g}/\text{mL}$ (1 mg diluted in 40 mL normal saline) via the proximal port of a "J-extension" set using a syringe pump (Model 3300 IVAC Medical Systems, Tacoma, WA). All patients received an initial infusion of $0.025 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which was increased after 3 min to $0.050 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The maximum infusion rate administered was $0.15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The remifentanyl infusion was discontinued at birth or after perineal repair (e.g., episiotomy).

The visual analog pain scale (VAPS) was used to assess the level of pain. This consisted of a 10-cm horizontal line anchored at each end with the words "no pain" and "worse pain imaginable." The presence and intensity of respiratory depression was evaluated with the Respiratory Intervention Scale (RIS) (Appendix).¹⁹ The presence and intensity of sedation was evaluated with the Observer's Assessment of Alertness/Sedation (OAA/S) scale (Appendix).²⁰

The remifentanyl infusion was titrated to achieve a VAPS score ≤ 4 during contractions. This value was maintained throughout all the phases of labor by increasing the infusion rate each time this value was exceeded. The rate was increased in increments of $25 \mu\text{g}/\text{h}$ ($0.42 \mu\text{g}/\text{min}$ or $1 \text{ mL}/\text{h}$) every minute to achieve a visual analog scale score ≤ 4 or to the maximum infusion rate. If the systolic blood pressure or heart rate were decreased more than 20% of the baseline value, RIS > 0 , or OAA/S > 3 , the infusion

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rate was immediately reduced to the previous value until the above variables were reached. Supplemental oxygen was not administered.

One-on-one nursing was maintained throughout the remifentanyl infusion. The anesthesiologist dedicated to the labor and delivery unit titrated the infusion rate and was present during maternal and fetal monitoring. VAPS scores were obtained before commencing analgesia (baseline) and 5 and 30 min after initiation of analgesia. Scores were obtained between contractions, and women were asked to rate the worst pain they had felt during their last contraction. Maternal heart rate, arterial blood pressure, and SpO₂ were recorded by the anesthesiologist before commencing analgesia, 5 and 10 min after initiating the infusion, and 5 and 10 min after increasing or decreasing the infusion rate. Additionally, VAPS was assessed every time the patient complained of an increase in pain. Additional monitoring was performed for clinical indications during the course of labor.

Fetal heart rate (FHR) was recorded for 30 min before initiating the remifentanyl infusion, and for 30 min after each increase in infusion rate. An obstetrician assessed the FHR tracing by rating variability (1: absence of variability; 2: <5 bpm; 3: 6–25 bpm; 4: >25 bpm) according to current guidelines.²¹ If FHR variability was rated Class 1 or 2, the infusion rate was reduced to the previous level. The infusion was stopped if fetal status was assessed as nonreassuring.

The Apgar scores at 1- and 5-min and neonatal naloxone administration were recorded, and umbilical artery pH was measured. Women were asked throughout labor to report side effects (e.g., nausea). Objective signs (vomiting, sedation, respiratory depression) were recorded by the labor nurse and the anesthesiologist. Overall satisfaction with analgesia was assessed by a second anesthesiologist on postpartum Day 1 using a 4-point verbal scale ranging from very satisfied to very dissatisfied (1: very dissatisfied, 2: dissatisfied, 3: satisfied, 4: very satisfied).

Data were collected by one anesthesiologist and summarized using descriptive statistics.

RESULTS

Two hundred sixteen women were enrolled in the study and 205 women received IV remifentanyl during labor. Table 1 shows the demographic, labor, and delivery data included in the analyses. The remifentanyl infusion rate range varied between 0.025 and 0.15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Table 2). The median infusion duration was 140 min (range, 35–1010 min). The VAPS and the degree of satisfaction are shown in Table 3.

Three patients complained of nausea, and no patient had vomiting, dizziness, pruritus, or confusion. Arterial blood pressure and heart rate were maintained within 20% of baseline values in all women for the entire duration. In no case was remifentanyl reduced or stopped for side effects. All parturients had RIS = 0. The

Table 1. Demographic, Labor, and Delivery Data

Age (yr)	33.6 ± 5.4
Weight (kg)	72 ± 10
Nulliparous	143 (70)
Labor spontaneous/induced	168/37 (82/18)
Cervical dilatation infusion start (cm)	4 (2–10)
Duration of infusion (min)	200 ± 170
Delivery characteristics	
Spontaneous vaginal	150 (73)
Kristeller maneuver ^a	7 (30)
Vacuum extraction	9 (4)
Episiotomy	22 (11)
Cesarean	17 (8)

Data are expressed as mean ± sd or n (%). Cervical dilation is expressed as median and range.

^a Manual pressure on the fundus of the uterus toward the birth canal with the aim to expedite delivery of the baby in the second stage of vaginal birth.

Table 2. Distribution of Patients per Maximum Infusion Rate

Infusion rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Number of women
0.025	6 (2.9)
0.050	38 (18.5)
0.075	61 (29.8)
0.100	69 (33.7)
0.125	11 (5.4)
0.150	20 (9.7)

Data are expressed as n (%).

Table 3. Visual Analog Pain Scale Scores and Degree of Satisfaction

VAPS (cm)	
Baseline	9.4 ± 1.2
5 min	5.1 ± 0.4
30 min	3.6 ± 1.5
Satisfaction score	
Very dissatisfied	12 (6)
Dissatisfied	14 (7)
Satisfied	143 (70)
Very Satisfied	36 (18)

Visual Analog Pain Scale (VAPS) measured before commencing analgesia (baseline), and 5-min and 10-min after initiating analgesia. Data expressed as mean ± sd or n (%).

mean SpO₂ was 98% ± 1%. SpO₂ was above 95% in all patients. None of the patients required oxygen supplementation or administration of naloxone. Eight patients (4%) had OAA/S Grade 2–3. None had OAA/S >3.

No changes in FHR variability score were observed between baseline tracings and those recorded after initiating the infusion or increasing the rate. Observed FHR changes during labor were judged independent of the remifentanyl infusion. The mean value of umbilical artery pH was 7.3 ± 0.1. Five infants had pH values of <7.1 (three with anhydramnios and two with fetal macrosomia). The median 1- and 5-min Apgar scores were 9 (range, 5–10) and 9 (range, 8–10), respectively. The lowest values were recorded in the five patients mentioned above. No neonate received naloxone. Most patients (87%) were satisfied with their analgesia (Table 3).

DISCUSSION

Studies reported in the literature on the use of remifentanyl for labor analgesia have described various administration methods and inconsistent results.

Remifentanyl has uniformly been administered using a patient-controlled IV analgesic technique with^{6,8,10,14,15} or without^{2,5,7-9,11,12,16-18} a basal infusion. Bolus doses have generally ranged from 0.2 to 0.8 $\mu\text{g}/\text{kg}$ and lockout intervals from 1 to 3 min, and a background infusion ranged from 0 to 0.15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Higher doses and shorter lockout intervals were correlated with a better analgesic efficacy, but were associated with more maternal side effects, such as sedation, nausea, and vomiting, and some cases of respiratory depression. Conversely, lower doses and longer lockout intervals were associated with a reduced incidence of side effects but less analgesic efficacy.

These findings suggest that fixed-dose regimens can lead to underdosing and inadequate analgesia or can lead to overdosing and maternal oxygen desaturation. In a volunteer study, the risk of respiratory depression appeared later than electroencephalogram depression after a remifentanyl bolus; the $T_{1/2}$ for respiratory depression was 2.5 min.²² This may explain the finding of respiratory depression in laboring women, because the peak of respiratory depression after a remifentanyl bolus (administered at the beginning of a contraction) may occur between contractions. Although further studies are needed to assess the effect of remifentanyl on the progress of labor, analgesia during the second stage of labor, and reasons for patient dissatisfaction, the data collected in this observational study show that continuous IV remifentanyl titrated to VAPS score may be a valid option for labor analgesia with few side effects.

APPENDIX

Respiratory Intervention Scale (RIS): score definition

- 0 = Pulse oximeter reading (SpO_2) above 90%. No intervention required
- 1 = $\text{SpO}_2 \geq 86\%$ but $\leq 90\%$ for >5 s. No intervention required but may consider rapid intervention if necessary
- 2 = $\text{SpO}_2 \leq 85\%$ for 5 s. Verbal prompts (up to three prompts to take a breath restored the $\text{SpO}_2 > 85\%$)
- 3 = After three verbal prompts to take a breath failed to restore SpO_2 to $>85\%$ for 5 s. Oxygen 2 L/min was applied via a nasal cannula and restored the SpO_2 to $>85\%$
- 4 = Intervention 3 failed to restore SpO_2 to $>85\%$ for 5 s. A verbal prompt to take a deep breath with nasal oxygen in place was made and restored SpO_2 to $>85\%$
- 5 = Intervention 4 failed to restore SpO_2 to $>85\%$ for 5 s. A tactile and verbal stimulus to breath was made and restored SpO_2 to $>85\%$
- 6 = Intervention 5 failed to restore SpO_2 to $>85\%$. Naloxone 0.4 mg was given to reverse hypoxemia. Positive-pressure ventilation with oxygen 100% by bag and mask was delivered if needed

Observer Assessment Alertness/Sedation Scale: score definition

- 1 = Awake and alert
- 2 = Drowsy with ptosis of eyelids
- 3 = Asleep but awakens with verbal stimulation
- 4 = Responds to tactile stimulation (tap on shoulder)
- 5 = Unresponsive to verbal or tactile stimulation intervention

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