Systemic Remifentanil for Labor Analgesia

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There is a need for safe, effective, and easy-to-administer systemic analgesia that ideally has rapid onset and offset, matches the time course of uterine contractions, and does not compromise the fetus. Although neuraxial blockade is the “gold standard” for labor analgesia, systemic analgesia is useful in those cases in which neuraxial analgesia is contraindicated, refused or simply not needed by the parturient, or when skilled anesthesia providers are not available. Because of its unique pharmacologic properties, remifentanil has been investigated, and is used clinically, to provide IV labor analgesia. In this focused review, we summarize the efficacy of remifentanil as a labor analgesic and review the current literature regarding its dose, mode of delivery, safety for the mother and fetus/neonate, as well as the scope for future research.

Satisfactory analgesia is of paramount importance in labor. Although neuraxial analgesia provides excellent analgesia, systemic analgesia is useful for parturients in whom neuraxial analgesia is contraindicated, refused or simply not needed, or when skilled anesthesia providers are not available. Meperidine (pethidine) is one of the most frequently used systemic opioids for labor analgesia, but it is far from ideal because it provides only modest analgesia. Side effects of meperidine include dysphoria, and accumulation of active metabolites impair alertness and create breast-feeding problems in the neonate. Hence, there is a need to find a suitable alternative. In this context, remifentanil delivered by a patient-controlled IV analgesia (PCIA) infusion system under nursing supervision may fill this role.

REMIFENTANIL PHARMACOKINETICS

Remifentanil is a 4-anilido-piperidine with an ester linkage susceptible to plasma and tissue esterase metabolism. It is an ultra short-acting mu-1 opioid receptor agonist with a rapid onset of action and a biexponential decay curve. Remifentanil has a small volume of distribution of 0.39 L/kg (SD ±0.25) with a rapid redistribution phase of 0.94 (SD ±0.57) min, and a short elimination half-life of 9.5 (SD ±4) min. Blood-brain equilibration occurs in 1.2–1.4 min. It is metabolized to an inactive metabolite by plasma and tissue esterases. The context-sensitive half-life of remifentanil is 3.5 min and is independent of the duration of the infusion. The analgesic half-life is 6 min, thus allowing effective analgesia for several consecutive painful uterine contractions. In theory, the rapid onset of analgesia (approximately 30–60 s), which peaks at 2.5 min, offers advantage for labor analgesia. The timing of delivery of each remifentanil PCIA dose is of crucial importance, and an IV bolus dose delivered at the beginning of a contraction (lasting on average 70 s) is likely to provide analgesia for the following contraction. Remifentanil plasma concentrations in pregnant women are approximately half those found in non-pregnant patients because of the greater volume of distribution and higher clearance. It crosses the placenta rapidly with a mean umbilical vein to maternal artery concentration ratio of 0.88. However, the mean umbilical artery to umbilical vein concentration ratio is 0.29, demonstrating that the drug is rapidly metabolized and redistributed in the fetus. This pharmacokinetic profile gives remifentanil an advantage over other opioids used for labor analgesia.

CLINICAL PRACTICE

Analgesic Efficacy

Four observational studies have evaluated remifentanil PCIA for first-stage labor analgesia, all reporting analgesia with the drug, but only modest reductions in pain scores (Table 1). Most studies have not assessed the analgesic efficacy of remifentanil in the second stage of labor, but when reported, the pain scores have remained high at approximately 80 mm (100 mm visual analog scale).
Other studies have compared the efficacy of remifentanil with other drugs, including meperidine, nitrous oxide, and epidural levobupivacaine. Blair et al. evaluated remifentanil PCA versus meperidine PCA and found that visual analog pain scores were similar, although patient satisfaction was higher with remifentanil. This was the only study that used a fixed dose (40 μg) rather than a weight-based dose. Thurlow et al. compared remifentanil with IM meperidine and showed significantly lower median pain scores with remifentanil (48 vs 72 mm). In a double-blind, randomized, controlled trial, Evron et al. compared the analgesic effect of remifentanil PCA with an IV infusion of meperidine in early labor. Remifentanil PCA achieved more effective analgesia for labor than IV meperidine. The visual analog score decrease in median pain scores with remifentanil was higher (36 vs 59 mm) and patient satisfaction was better (72 vs 64). In another study, Balki et al. compared remifentanil PCA (0.2–1.0 g/kg; the most frequent dose was 0.5 g/kg). Volikas et al. found that a dose of 0.5 μg/kg with a 2-min lockout was effective in significantly decreasing pain scores by a mean of 23 mm from baseline in 86% of patients. Most studies report a wide interindividual variation in the bolus dose required to achieve effective analgesia, suggesting that a fixed-dose regimen could potentially underdose (leading to analgesia failure) or overdose (causing side effects such as maternal oxygen desaturation). Indeed, the study by Blair et al. using a 40-μg remifentanil fixed dose found no differences in pain scores compared with meperidine PCA, in contrast to other variable dose studies. This interindividual variation in analgesia requirements also means that pain scores could potentially be improved if the remifentanil bolus dose was titrated against response rather than being fixed. This approach also allows for the escalation of pain typically observed during labor. Evron et al. used a regimen that involved an initial bolus of 20 μg, regardless of patient weight, with a 3-min lockout, followed by an increase in the bolus dose of 5 μg every 15 min on patient request until adequate analgesia was achieved.

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Table 1. Summary of Remifentanil Studies for Labor Analgesia

<table>
<thead>
<tr>
<th>Remifentanil PCA bolus dose</th>
<th>No.</th>
<th>Comparator group</th>
<th>Lockout interval (min)</th>
<th>Nitrous oxide used</th>
<th>Median or reduction in pain scores</th>
<th>Conversion to neuraxial analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair et al.14</td>
<td>21</td>
<td>None</td>
<td>2</td>
<td>No</td>
<td>Median 50 mm</td>
<td>4 of 21</td>
</tr>
<tr>
<td>Thurlow et al.16</td>
<td>18</td>
<td>IM meperidine</td>
<td>2</td>
<td>Yes</td>
<td>Median 48 mm</td>
<td>7 of 18</td>
</tr>
<tr>
<td>Volmanen et al.18</td>
<td>20</td>
<td>Nitrous oxide</td>
<td>1</td>
<td>Reduction of 15 mm</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Blair et al.15</td>
<td>17</td>
<td>PCIA meperidine</td>
<td>2</td>
<td>Yes</td>
<td>Median 64 mm</td>
<td>2 of 20</td>
</tr>
<tr>
<td>Volmanen et al.13</td>
<td>17</td>
<td>None</td>
<td>1</td>
<td>No</td>
<td>Reduction of 42 mm</td>
<td>Not reported</td>
</tr>
<tr>
<td>Evron et al.17</td>
<td>43</td>
<td>Meperidine infusion</td>
<td>3</td>
<td>No</td>
<td>Median 35 mm</td>
<td>4 of 43</td>
</tr>
<tr>
<td>Volikas et al.12</td>
<td>50</td>
<td>None</td>
<td>2</td>
<td>No</td>
<td>Mean 46 mm</td>
<td>5 of 50</td>
</tr>
<tr>
<td>Balki et al.31</td>
<td>10</td>
<td>Variable infusion +</td>
<td>2</td>
<td>No</td>
<td>Reduction of 56 mm</td>
<td>1 of 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fixed IV infusion +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>fixed IV bolus</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All pain scores reported in millimeter (0–100 mm scale) for comparison between studies.

PCIA = patient-controlled IV analgesia.

mean that many women are satisfied with this type of analgesia in the first stage of labor. Despite the modest quality of analgesia from remifentanil, other aspects of the birth experience, particularly the timing of the analgesia and inclusion in the obstetric decision making, are important to many parturients and likely influence overall satisfaction.

**Optimal Dosing Regimen**

The efficacy of remifentanil may depend on both the dose and manner in which it is administered. Remifentanil can be given as an intermittent patient-administered bolus with a lockout interval and with or without a background infusion. The timing of dose administration, the rate of bolus delivery, and the lockout interval are important to analgesia outcome, and research is continuing in this area. Each study had a unique dosing schedule (Table 1) with the bolus dose varying between 0.2 to 0.93 μg/kg; the most frequent dose was 0.5 μg/kg. Volikas et al. found that a dose of 0.5 μg/kg with a 2-min lockout was effective in significantly decreasing pain scores by a mean of 23 mm from baseline in 86% of patients. Most studies report a wide interindividual variation in the bolus dose required to achieve effective analgesia, suggesting that a fixed-dose regimen could potentially underdose (leading to analgesia failure) or overdose (causing side effects such as maternal oxygen desaturation). Indeed, the study by Blair et al. using a 40-μg remifentanil fixed dose found no differences in pain scores compared with meperidine PCA, in contrast to other variable dose studies. This interindividual variation in analgesia requirements also means that pain scores could potentially be improved if the remifentanil bolus dose was titrated against response rather than being fixed. This approach also allows for the escalation of pain typically observed during labor. Evron et al. used a regimen that involved an initial bolus of 20 μg, regardless of patient weight, with a 3-min lockout, followed by an increase in the bolus dose of 5 μg every 15 min on patient request until adequate analgesia was achieved.

It seems that remifentanil produces clinically effective, but not complete, analgesia, with conversion rates to neuraxial analgesia < 10% (Table 1). This may
Another important aspect of achieving adequate pain relief with remifentanil in labor is the timing and rate of administration of the bolus dose. Blair et al.15 delivered the remifentanil bolus dose in “stat” mode through the PCIA device over 18 s, whereas other investigators administered a bolus over 1 min.13,19 Lockout intervals have also varied from 1 to 3 min (Table 1).

According to computer simulations and pharmaco-dynamic studies in nonobstetric populations, the peak central nervous system effect of a bolus dose of remifentanil occurs in 1–3 min after a rapid IV bolus.8,20,21 Therefore, if a single bolus of remifentanil is delivered at the beginning of a uterine contraction, it is likely to exert its peak effect during the next contraction.

It is unclear whether PCIA with a background infusion confers any analgesic advantage. Blair et al.14 reported that a background infusion of remifentanil did not improve analgesia but caused more maternal side effects. In contrast, Balki et al.11 recommended a PCIA bolus dose of 0.25 µg·kg⁻¹·min⁻¹ with a background infusion of 0.025–0.1 µg·kg⁻¹·min⁻¹, claiming only a 5% neuraxial analgesia conversion rate (Table 1). More work is needed to establish the optimal drug administration regimen for remifentanil in labor.

### Maternal Effects

The use of opioids in labor is frequently limited by maternal side effects, including sedation, hypventilation, oxygen desaturation, and nausea and vomiting. Remifentanil’s fast onset and offset allows easy titration as well as rapid elimination from the parturient and the fetus/neonate, which in theory reduces concerns regarding adverse effects. Most studies have reported maternal desaturation requiring oxygen supplementation that is short lived, as well as maternal sedation (Table 2).12–14

<table>
<thead>
<tr>
<th>Remifentanil bolus dose</th>
<th>Maternal desaturation episodes</th>
<th>FHR abnormalities</th>
<th>Appgar scores at 1 and 5 min</th>
<th>Umbilical artery pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair et al.14</td>
<td>0.25–0.5 µg·kg⁻¹·min⁻¹</td>
<td>2 of 21</td>
<td>4 of 21 (Sao₂ &lt;90%)</td>
<td>2 of 21 (probably unrelated to drug)</td>
</tr>
<tr>
<td>Thurlow et al.16</td>
<td>0.2 µg·kg⁻¹·min⁻¹</td>
<td>Not reported</td>
<td>7 of 18 (Sao₂ &lt;94%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Volmanen et al.18</td>
<td>0.4 µg·kg⁻¹·min⁻¹</td>
<td>Increased sedation scores versus N₂O</td>
<td>0 of 43 (Sao₂ &lt;94%); patients on supplemental O₂</td>
<td>4 of 43</td>
</tr>
<tr>
<td>Blair et al.15</td>
<td>40 µg</td>
<td>Low incidence; similar to meperidine</td>
<td>Similar to meperidine</td>
<td>1 of 15</td>
</tr>
<tr>
<td>Volmanen et al.13</td>
<td>0.2–0.8 µg·kg⁻¹·min⁻¹</td>
<td>17 of 17; mild sedation</td>
<td>10 of 17 (Sao₂ &lt;94%)</td>
<td>5 of 17</td>
</tr>
<tr>
<td>Evron et al.17</td>
<td>0.27–0.93 µg·kg⁻¹·min⁻¹</td>
<td>0 of 43</td>
<td>0 of 43 (Sao₂ &lt;94%)</td>
<td>4 of 43</td>
</tr>
<tr>
<td>Volikas et al.12</td>
<td>0.5 µg·kg⁻¹·min⁻¹</td>
<td>22 of 50; mild sedation</td>
<td>0 of 50 (Sao₂ &lt;93%)</td>
<td>10 of 50</td>
</tr>
<tr>
<td>Balki et al.11</td>
<td>0.25–1.0 µg·kg⁻¹·min⁻¹</td>
<td>10 of 10</td>
<td>6 of 10 (Sao₂ &lt;95%)</td>
<td>2 of 10</td>
</tr>
<tr>
<td>+ fixed IV infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volmanen et al.19</td>
<td>0.3–0.7 µg·kg⁻¹·min⁻¹</td>
<td>7 of 24</td>
<td>13 of 24 (Sao₂ &lt;95%)</td>
<td>13 of 24</td>
</tr>
</tbody>
</table>

FHR = fetal heart rate.

Comparative studies help us to put maternal desaturation with remifentanil into context. Blair et al.15 found a similar incidence of desaturation when remifentanil PCIA was compared with meperidine PCIA. The study by Evron et al.17 showed a significantly lower maternal oxygen saturation with IV meperidine compared with remifentanil (94.2% vs 97.5%), although it should be mentioned that supplemental oxygen was given to parturients whenever the oxygen saturation decreased to <95%. Eight patients in the meperidine group and none in the remifentanil group had decreases in oxygen saturation to <95%. (Interestingly, in a study that included parturients receiving either meperidine/Entonox, epidural bupivacaine/fentanyl mixtures, plain epidural bupivacaine, or no analgesia for labor, the group that had no analgesia had the highest incidence of desaturation in the active second stage of labor.12)

Sedation has also been reported during remifentanil analgesia, but it is rarely excessive (Table 2). Nausea and vomiting is a recognized effect of opioid analgesia. The incidence reported with remifentanil has ranged from 0%17 to as high as 60%.11

### Fetal and Neonatal Effects

Because remifentanil is a potent opioid, there is concern about neonatal depression, fetal heart rate (FHR) abnormalities, and drug accumulation in the neonate. Fewer nonassuring FHR patterns and better neurobehavioral scores were found with remifentanil PCIA compared with meperidine PCIA (Table 2).15 Volikas et al.12 reported that the incidence of FHR abnormalities was low and no obstetric interventions were required. Maternal vein and umbilical cord blood samples showed small amounts of placental transfer of remifentanil unlikely to be of clinical significance, and umbilical cord blood gas values were within the normal range. In the study by Evron et al.,17
FHR remained reactive in 90% in the remifentanil group versus 38% in the meperidine group.

No study has identified an increased incidence of nonreassuring FHR recordings after remifentanil has been used for labor analgesia. Apgar scores and umbilical cord gases have all been within normal limits. Furthermore, no neonate has needed naloxone after delivery, confirming remifentanil’s rapid metabolism and redistribution in the neonate after placental transfer.

Concomitant Use of Nitrous Oxide During Remifentanil Labor Analgesia

Remifentanil provided superior analgesia to 50% nitrous oxide (Entonox) when administered to women in a small crossover study with a threefold reduction in median pain scores (15 vs 5 mm). Two studies comparing remifentanil PCA with meperidine PCA allowed parturients to use nitrous oxide to supplement opioid analgesia as part of the study protocol. Thurlow et al. found equal use of nitrous oxide in the IM meperidine and remifentanil PCA groups. Blair et al. derived a similar conclusion: 19 of 19 women in the meperidine group and 18 of 20 in the remifentanil group chose to continue to use nitrous oxide. It seems that when given the choice, women frequently prefer to continue using nitrous oxide at the same time as remifentanil PCA, although some studies of systemic opioid analgesia have identified an increased risk of hypoxemia with the addition of nitrous oxide.

Supervision and Monitoring

The findings of various studies point to the need for close (one-to-one nursing/midwife) patient supervision, training for the caregiver such as the labor nurse, continuous oxygen saturation monitoring, and a dedicated IV cannula while a parturient is receiving a remifentanil PCA regimen. Suggested guidelines for the use of remifentanil PCA for labor analgesia are shown in Table 3.

Future Research

Optimal remifentanil PCA regimens may well require titration against individual patient response as well as a titration in dose requirements as labor progresses. Further developments may include synchronization of the remifentanil PCA bolus dose to the tocodynamometer recording so that the maximum analgesic effect of the drug may occur at the peak of the uterine contraction. Administration of the bolus during the period between contractions may also potentially improve efficacy.

CONCLUSION

There is evidence supporting the analgesic effects and suitability of remifentanil for first-stage labor analgesia, although the timing of the onset of action or peak action cannot currently be matched to uterine contraction pain. Although remifentanil provides only modest analgesia, it seems to be popular with parturients enrolled in trials. An appropriate PCA dose regimen is a 40-μg bolus with a 2-min lockout. Because of its side-effect profile, guidelines should be in place to ensure routine oxygen saturation monitoring, oxygen supplementation if needed to treat maternal desaturation, and one-to-one nursing/midwife monitoring using trained personnel. The requirement for close monitoring is a potential drawback to routine use of the technique in a clinical setting. We believe that remifentanil PCA for labor analgesia is an important advance in the obstetric anesthesia armamentarium, especially for parturients who do not want neuraxial analgesia or when its use is contraindicated.

**References**


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**Table 3. Suggested Guidelines for Patient-Controlled IV Analgesia (PCA) with Remifentanil**

<table>
<thead>
<tr>
<th>Eligibility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td></td>
</tr>
<tr>
<td>No opioid use in the previous 4 h</td>
<td></td>
</tr>
<tr>
<td>Dedicated IV cannula for remifentanil administration</td>
<td></td>
</tr>
</tbody>
</table>

**PCA protocol**

- **PCIA bolus:** 40 μg
- **Lockout interval:** 2 min

**Continuous observations**

- SaO₂ (pulse oximetry)
- Nursing supervision: one-to-one

**30-min observations**

- Respiratory rate
- Sedation score
- Pain score

**Indications for contacting the anesthesia provider**

- Excessive sedation score (not arousable to voice)
- Respiratory rate <8 breaths/min
- SaO₂ <90% while breathing room air

Sample guidelines adapted from those used by the Ulster Community and Hospitals Trust, Ulster, United Kingdom. Labor nurses must establish competency in the use of remifentanil PCA before providing care.

**PCA = patient-controlled IV analgesia.**
24. Volmanen P, Akural S, Alahuhta S. In early labour, IVPCA remifentanil bolus during the contraction pause does not improve the analgesic effect but reduces sedation compared with bolus given during the uterine contraction. Eur J Anaesthesiol 2009;26:11AP1–4