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.

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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,[1] but it is far from ideal because it provides only modest analgesia.[2] Side effects of meperidine include dysphoria, and accumulation of active metabolites impair alertness and create breast-feeding problems in the neonate.[3–5] 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.[6] 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.[7] 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[8], 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.[9] 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.[10] 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).[11–14] 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).[14]

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Table 1. Summary of Remifentanil Studies for Labor Analgesia

	Remifentanil PCIA bolus dose	No.	Comparator group	Lockout interval (min)	Nitrous oxide used	Median or reduction in pain scores	Conversion to neuraxial analgesia
Blair et al.[14]	0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	21	None	2	No	Median 50 mm	4 of 21
Thurlow et al.[16]	0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	18	IM meperidine	2	Yes	Median 48 mm	7 of 18
Volmanen et al.[18]	0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$	20	Nitrous oxide	1		Reduction of 15 mm	Not reported
Blair et al.[15]	40 μg	20	PCIA meperidine	2	Yes	Median 64 mm	2 of 20
Volmanen et al.[13]	0.2–0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$	17	None	1	No	Reduction of 42 mm	Not reported
Evron et al.[17]	0.27–0.93 $\mu g \cdot kg^{-1} \cdot min^{-1}$	43	Meperidine infusion	3	No	Median 35 mm	4 of 43
Volikas et al.[12]	0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	50	None	2	No	Mean 46 mm	5 of 50
Balki et al.[11]	0.25–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ variable bolus + fixed IV infusion	10	0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ variable infusion + fixed IV bolus	2	No	Reduction of 56 mm vs 41 mm(variable bolus versus variable infusion)	1 of 20
Volmanen et al.[19]	0.3–0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$	24	Epidural	1	No	Median 73 mm	Not reported

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

PCIA = patient-controlled IV analgesia.

Other studies have compared the efficacy of remifentanil with other drugs, including meperidine,[15–17] nitrous oxide,[18] and epidural levobupivacaine.[19] Blair et al.[15] evaluated remifentanil PCIA versus meperidine PCIA 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.[16] 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.[17] compared the analgesic effect of remifentanil PCIA with an IV infusion of meperidine in early labor. Remifentanil PCIA achieved more effective analgesia for labor than IV meperidine. The visual analog score was lower (36 vs 59 mm) and patient satisfaction was higher (3.9 vs 1.9 using a 4-point scale, 1 = poor and 4 = excellent analgesia) in the remifentanil group. The need to convert to epidural analgesia because of inadequate pain relief was less with remifentanil (11% vs 39%). In a double-blind crossover trial, Volmanen et al.[18] compared remifentanil PCIA (0.40 μg/kg bolus) with 50% nitrous oxide and showed a threefold decrease in median pain scores with remifentanil compared with nitrous oxide (1.5 vs 0.5). In another double-blind randomized study, Volmanen et al.[19] compared remifentanil PCIA (mean effective dose 0.5 μg/kg with 1-min lockout) with 20 mL epidural levobupivacaine (0.625 mg/mL with 2 μg/mL fentanyl) and found lower pain scores with levobupivacaine (5.2 vs 7.3) but surprisingly no significant differences in pain relief scores between the groups. The authors speculated that the results could be explained by the sedative and euphoric effect of opioids, which caused the parturients to tolerate high pain scores.[19] There is little doubt that epidural analgesia leads to superior pain relief, but remifentanil may make labor pain more acceptable.

It seems that remifentanil produces clinically effective, but not complete, analgesia, with conversion rates to neuraxial analgesia <10% (Table 1). This may 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.[12] 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.[15] using a 40-μg remifentanil fixed dose found no differences in pain scores compared with meperidine PCIA, 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.[17] 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.

Table 2. Maternal and Neonatal Effects of Remifentanil

	Remifentanil bolus dose	Maternal sedation	Maternal desaturation episodes	FHR abnormalities	Apgar scores at 1 and 5 min	Umbilical artery pH
Blair et al.[14]	0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	2 of 21	4 of 21 (Sao_2 <90%)	2 of 21 (probably unrelated to drug)	Median 8, 9	Mean 7.34
Thurlow et al.[16]	0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Not reported	7 of 18 (Sao_2 <94%)	Not reported	Not reported	Not reported
Volmanen et al.[18]	0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Increased sedation scores versus N_2O	None (Sao_2 <93%); patients on supplemental O_2	3 of 15	Median 9, 9	Not reported
Blair et al.[15]	40 μg	Low incidence; similar to meperidine	Similar to meperidine	1 of 15	Median 8, 9	Median 7.32
Volmanen et al.[13]	0.2–0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$	17 of 17; mild sedation	10 of 17 (Sao_2 <94%)	5 of 17	Range 8–10; in 16 of 17	pH >7.1 in 15 of 17
Evron et al.[17]	0.27–0.93 $\mu g \cdot kg^{-1} \cdot min^{-1}$	0 of 43	0 of 43 (Sao_2 <94%)	4 of 43	0 of 43; <7	Mean 7.3
Volikas et al.[12]	0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	22 of 50; mild sedation	0 of 50 (Sao_2 <93%)	10 of 50	Median 9, 9	Median 7.3
Balki et al.[11]	0.25–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + fixed IV infusion	10 of 10	6 of 10 (Sao_2 <95%)	2 of 10	Mean >7; in 10 of 10; <9 in 1	Mean 7.24
Volmanen et al.[19]	0.3–0.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$	7 of 24	13 of 24 (Sao_2 <95%)	13 of 24	Median 9	Median 7.25

FHR = fetal heart rate.

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 pharmacodynamic 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 (2-min lockout) with a background infusion of 0.025–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 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, hypoventilation, 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]

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.[22])

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 nonreassuring 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).[18] Two studies comparing remifentanil PCIA with meperidine PCIA allowed parturients to use nitrous oxide to supplement opioid analgesia as part of the study protocol.[15,16] Thurlow et al.[16] found equal use of nitrous oxide in the IM meperidine and remifentanil PCIA groups. Blair et al.[15] 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 PCIA, although some studies of systemic opioid analgesia have identified an increased risk of hypoxemia with the addition of nitrous oxide.[23]

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 PCIA regimen. Suggested guidelines for the use of remifentanil PCIA for labor analgesia are shown in Table 3.

Future Research

Optimal remifentanil PCIA 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 PCIA bolus dose to the tocodynameter recording so that the maximum analgesic effect of the drug can occur at the peak of the uterine contraction. Administration of the bolus during the period between contractions may also potentially improve efficacy.[24]

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.[1] An appropriate PCIA dose regimen is a 40-μg bolus with a 2-min lockout.[9] 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 PCIA 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.

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

Eligibility
Informed consent
No opioid use in the previous 4 h
Dedicated IV cannula for remifentanil administration
PCIA protocol
PCIA bolus: 40 μg
Lockout interval: 2 min
Continuous observations
SaO_2 (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
SaO_2 <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 PCIA before providing care.

PCIA = patient-controlled IV analgesia.

REFERENCES

1. Saravanakumar K, Garstang JS, Hasan K. Intravenous patient-controlled analgesia for labour: a survey of UK practice. Int J Obstet Anesth 2007;16:221–5
2. Tsui MH, Ngan Kee WD, Ng FF, Lau TK. A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. BJOG 2004; 111:648–55
3. Belsey EM, Rosenblatt DB, Lieberman BA, Redshaw M, Caldwell J, Notarianni L, Smith RL, Beard RW. The influence of maternal analgesia on neonatal behaviour: I. Pethidine. Br J Obstet Gynaecol 1981;88:398–406
4. Evron S, Ezri T. Options for systemic labor analgesia. Curr Opin Anaesthesiol 2007;20:181–5
5. Nissen E, Widstrom AM, Lilja G, Matthiesen AS, Uvnas-Moberg K, Jacobsson G, Boreus LO. Effects of routinely given pethidine during labour on infants' developing breastfeeding behaviour. Effects of dose-delivery time interval and various concentrations of pethidine/norpethidine in cord plasma. Acta Paediatr 1997;86:201–8
6. Glass PS, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, Grosse CM, Hermann D. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). Anesth Analg 1993;77:1031–40
7. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. Curr Opin Anaesthesiol 2000;13:449–55

8. Babenco HD, Conard PF, Gross JB. The pharmacodynamic effect of a remifentanil bolus on ventilatory control. Anesthesiology 2000;92:393–8
9. Hill D. The use of remifentanil in obstetrics. Anesthesiol Clin 2008;26:169–82
10. Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology 1998;88:1467–74
11. Balki M, Kasodekar S, Dhumne S, Bernstein P, Carvalho JC. Remifentanil patient-controlled analgesia for labour: optimizing drug delivery regimens. Can J Anaesth 2007;54:626–33
12. Volikas I, Butwick A, Wilkinson C, Pleming A, Nicholson G. Maternal and neonatal side-effects of remifentanil patient-controlled analgesia in labour. Br J Anaesth 2005;95:504–9
13. Volmanen P, Akural EI, Raudaskoski T, Alahuhta S. Remifentanil in obstetric analgesia: a dose-finding study. Anesth Analg 2002;94:913–7
14. Blair JM, Hill DA, Fee JP. Patient-controlled analgesia for labour using remifentanil: a feasibility study. Br J Anaesth 2001;87: 415–20
15. Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JP. Patient controlled analgesia for labour: a comparison of remifentanil with pethidine. Anaesthesia 2005;60:22–7
16. Thurlow JA, Laxton CH, Dick A, Waterhouse P, Sherman L, Goodman NW. Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. Br J Anaesth 2002;88:374–8
17. Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Remifentanil: a novel systemic analgesic for labor pain. Anesth Analg 2005; 100:233–8
18. Volmanen P, Akural E, Raudaskoski T, Ohtonen P, Alahuhta S. Comparison of remifentanil and nitrous oxide in labour analgesia. Acta Anaesthesiol Scand 2005;49:453–8
19. Volmanen P, Sarvela J, Akural EI, Raudaskoski T, Korttila K, Alahuhta S. Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. Acta Anaesthesiol Scand 2008;52:249–55
20. Egan TD, Minto CF, Hermann DJ, Barr J, Muir KT, Shafer SL. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. Anesthesiology 1996;84:821–33
21. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997;86:24–33
22. Griffin RP, Reynolds F. Maternal hypoxaemia during labour and delivery: the influence of analgesia and effect on neonatal outcome. Anaesthesia 1995;50:151–6
23. Reed PN, Colquhoun AD, Hanning CD. Maternal oxygenation during normal labour. Br J Anaesth 1989;62:316–8
24. Volmamen 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

