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REVIEW

Efficacy and Safety of Remifentanil as an Alternative Labor Analgesic

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Abstract: The objective of this review was to evaluate the clinical efficacy and safety of remifentanil in the management of labor pain. Although neuraxial analgesia is the best option during labor, alternative analgesic options are needed for patients with contraindications. Using a systematic literature search, clinical outcomes of remifentanil for labor pain have been summarized. Also, comparisons of remifentanil to other options including meperidine, epidural analgesia, fentanyl, and nitrous oxide are provided. Based on the literature review, remifentanil is associated with high overall maternal satisfaction and favorable side-effect profile. However, due to the low reporting of adverse events, large, randomized controlled trials are needed to evaluate maternal and neonatal safety adequately and determine the optimal dosing needed to provide effective analgesia. While remifentanil is a feasible alternative for patients who cannot or do not want to receive epidural analgesia, administration should be monitored closely for potential adverse effects.

Keywords: labor analgesia, remifentanil, opioids

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Introduction

Some of the most common anesthetic procedures are performed during labor to provide satisfactory analgesia for the patient. In fact, correct timing and availability of analgesia are the most important factors for maternal satisfaction.[1] Many institutions use epidural analgesia since it is recommended as a first-line method and is the most effective method for pain relief during labor with minimal side effects.[2–4] However, epidural analgesia may not be best option for women with an absolute or relative contraindication including the following: (1) higher risk for thrombosis or thromboembolism receiving prophylactic anticoagulants, (2) former congenital heart correction surgery with need for life-long anticoagulation,[5] (3) infections, (4) bleeding disorders, (5) spinal abnormalities, or (6) maternal anxiety and/or preference. Alternative strategies for pain relief may be necessary in patients where administration of epidural analgesia may be technically difficult (eg, obese patients who generally have a lower success rate with this technique).[6]

Due to concern for contraindications and limited availability of epidural analgesia, systemic opioids have been used as an alternative with widespread and increasing use; however, their use has been criticized due to limited evidence for efficacy.[7–13] The use of systemic opioids is controversial since they can produce incomplete analgesia depending on the type and dose of drug combined with frequent neonatal and maternal side effects.[8,14] In the United States, parenteral opioids commonly used include meperidine (Demerol®), morphine, fentanyl (Sublimaze®), butorphanol (Stadol®), and nalbuphine (Nubain®).[10] In the United Kingdom[15] and Norway,[13] pethidine administered intramuscularly (another generic name for meperidine in Europe) is the most commonly used opioid during labor (43% in the United Kingdom and 77% in Norway). Also, in the United Kingdom, 49% of obstetric wards use patient-controlled analgesia (PCA), with remifentanil as the most common agent followed by morphine and fentanyl.[15] In Belgium, 36% of obstetric wards use opioid PCAs, with remifentanil being the most common (77%).[13]

Although meperidine is one of the most frequently used opioids,[15] it is not ideal since it provides only modest analgesia,[17] and it is associated with many problems such as accumulation of active metabolites causing sedation, dysphoria, and breast-feeding problems in the neonate.[10,18,19] Using fentanyl has been associated with up to a 44% incidence of neonates with low Apgar scores.[20] Also, due to its slow onset of action, fentanyl does not always provide adequate pain relief during the first stage of labor.[21] These disadvantages of opioid analgesics are more commonly observed during systemic administration of large doses to achieve pain relief. When used in epidural analgesic techniques, opioid analgesics are often used in relatively small doses with insignificant systemic effects. However, some opioid analgesics like fentanyl can achieve significant systemic concentrations due to their lipophilicity, which can increase the risk of side effects when used in epidural analgesic techniques. For management of labor pain, the ideal opioid should have a rapid onset and offset (regardless of route of administration), rapid metabolism and elimination, and minimal side effects to both the mother and neonate. Also, providing analgesia should not inhibit the mother's ability to participate actively in the labor.

The search for an ideal opioid that would overcome these issues led to the investigation of remifentanil for the management of labor pain.[22–24] Due to its unique pharmacodynamic and pharmacokinetic profile, remifentanil for use during pregnancy is gaining popularity.[13] The objective of this review was to evaluate the efficacy and safety of remifentanil patient-controlled infusion compared with other techniques and define its role in place of therapy for the management of labor pain.

Mechanisms of Action, Metabolism, and Pharmacokinetic Profile

Remifentanil is a novel agent that has been used in the past decade for surgical anesthesia, sedation for mechanically ventilated patients and postoperative analgesia.[25] Remifentanil belongs to the anilidopiperidine class of synthetic opioid. It is an ultra short-acting synthetic mu opioid receptor agonist characterized by rapid onset and offset of action.[26] Since it has a rapid effect, it is administered intravenously using a PCA at the beginning of an uterine contraction so that a peak effect can occur with the next one.[27] Remifentanil has a quick onset of action in 1 minute, peak effect at 2 minutes, duration of action for 20 minutes, and constant context-sensitive half-life of 3 minutes (independent of duration of infusion). Remifentanil is rapidly metabolized to an inactive

metabolite (remifentanil acid) by plasma and tissue esterases, and it is eliminated completely by tissue esterases in 9–10 minutes after administration.[28–30] Due to its rapid metabolism and elimination, it does not accumulate even after prolonged use.

After a similar intravenous dose, the plasma concentration in a pregnant woman is half that of a nonpregnant woman due to larger volume of distribution and higher clearance.[31] Blood-brain equilibration occurs in 1.2–1.4 minutes. Remifentanil crosses the placenta freely 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. This indicates that it is eliminated quickly in neonates by rapid metabolism and redistribution.[31,32] Because the need for analgesia increases as labor progresses and due to the difficulty in predicting time-to-clinical effect after analgesic administration, the rapid effect and elimination makes remifentanil a useful agent. Also, it can be appropriately titrated for administration depending on need for analgesia for brief or long period of time.

In order to administer remifentanil, venous access is needed, and a continuous-infusion pump with intravenous drip support and compatible syringes are used. The optimal method of administration and dosing regimen is unclear and remains under investigation.

Clinical Studies

Many clinical trials have been conducted to investigate the efficacy and safety of remifentanil for labor analgesia. Most studies included healthy women with no comorbidities experiencing full term pregnancy. The use of remifentanil for preterm labor analgesia has not been evaluated in these studies. 4 observational studies focused on remifentanil with no comparator analgesic (Table 1). Several studies used 1 of 4 different active comparators: (1) meperidine (Table 2), (2) epidural analgesia (Table 3), (3) fentanyl, and (4) nitrous oxide. For all studies, the primary outcomes focused on efficacy including pain scores after 1 hour of labor and conversion rate to neuraxial analgesia. Also, maternal and neonatal adverse effects after remifentanil administration were investigated as secondary outcomes. These adverse effects included maternal sedation and respiratory depression and fetal heart rate abnormalities and Apgar scores. These secondary outcomes have been summarized for all included studies in Table 4.

Clinical Efficacy

4 studies investigated the clinical efficacy of remifentanil for labor pain without using a comparator.[22,33–35] Table 1 summarizes these studies, describing the dosing strategy for remifentanil, mean pain scores after 1 hour of labor, and the incidence of conversion to neuraxial analgesia. 3 of these studies investigating remifentanil PCA used a stepwise approach and allowed patients to increase the dose depending on level of pain.[22,33,35] Volikas and colleagues used a fixed dose regimen when administering remifentanil PCA.[34] One study also investigated the use of continuous infusion for remifentanil.[33]

To assess the primary outcome, pain score, all studies used the Visual Analogue Scale (VAS) for pain (range from 0 to 100 mm).[22,33–35] Sedation was assessed using a 4-point scale (1 = awake and alert, 2 = awake but drowsy, 3 = drowsy but arousable, 4 = unarousable)[34,35] or a 5-point scale (1 = awake, 2 = drowsy, 3 = rousable to voice, 4 = rousable to touch, 5 = unrousable).[22,33] All except one study[33] did not use a background infusion in addition to the PCA when administering remifentanil intravenously.[22,34,35] Most studies excluded patients with multiple pregnancies,

Table 1. Summary of remifentanil observational studies evaluating clinical efficacy for labor analgesia.

Reference	N	Bolus (mcg/kg) or infusion (mcg/kg/min)	Lockout time (min)	Pain score post-intervention (total 100 mm)	Conversion to neuraxial analgesia (N)
Blair[22]	21	Bolus: 0.25–0.5	2	Median 50 mm Decrease of 30 mm[a]	19% (4/21)
D'Onofrio[33]	205	Infusion: 0.025–0.15	N/A	Mean 36 mm[b]	0%
Volikas[34]	50	Bolus: 0.5	2	Mean 46 mm[c]	10% (5/50)
Volmanen[35]	17	Bolus: 0.2–0.8	1	Decrease of 42 mm[d]	NR

Notes: [a]Statistically significant difference ($P < 0.05$); [b]statistical analyses not performed; [c]statistically significant difference ($P < 0.017$); [d]statistically significant difference ($P < 0.001$).
Abbreviations: N, number of patients; N/A, not applicable; NR, not reported.

Table 2. Remifentanil studies evaluating clinical efficacy for labor analgesia in comparison with meperidine.

Reference	Study design	N	Bolus (mcg/kg) or infusion (mcg/kg/min)	Lockout time (min)	Active comparator	Pain score post-intervention (total 100 mm)	Conversion to neuraxial analgesia (N)
Douma[36]	RCT	159	Bolus: 0.7 Infusion: 0.025	30	Meperidine Fentanyl	R: 45.6 mm[a] M: 66.1 mm F: 59.6 mm	13% (7/52)
Evron[37]	RCT	88	Bolus: 0.27–0.93	3	Meperidine	R: 35.8 mm[b] M: 58.8 mm	10.8% (5/43)
Shahriari[38]	RCT	40	Bolus: 0.35–0.7	4	Meperidine	R: 33 mm[b] M: 66 mm	NR
Thurlow[39]	RCT	36	Bolus: 0.3	3	Meperidine	R: 48 mm[b] M: 72 mm	39% (7/18)
Blair[23]	RCT	39	Bolus: 0.5	2	Meperidine	R: 64 mm[c] M: 69 mm	10% (2/20)
Ng[40]	RCT	68	Bolus: 0.37–0.44	3.75–4.5	Meperidine	R: 20 mm[b] M: 36 mm	0
Volikas[24]	RCT	17	Bolus: 0.5	2	Meperidine	R: 20 mm[b] M: 36 mm	11% (1/9)

Notes: [a]Statistically significant difference between remifentanil and meperidine ($P < 0.001$) and remifentanil and fentanyl ($P < 0.01$); [b]statistically significant difference ($P < 0.001$); [c]no statistically significant difference.
Abbreviations: N, number of patients; RCT, randomized controlled trial; R, remifentanil; M, meperidine; F, fentanyl; NR, not reported.

pre-eclampsia, or allergy to any agent under investigation.[22,33,34] Many studies concluded that remifentanil is safe and can lead to a significant reduction in pain scores from baseline by 20–58 mm in the first stage of labor in spite of being incomplete analgesia.[22,34,35] Many studies demonstrated that majority of mothers (62%–88%) had high satisfaction scores after remifentanil administration.[22,33,35] Significant limitations of these studies include small number of participants, short duration and infrequent collection of data, as well as inappropriate reporting of efficacy or side effects.[22,33–35]

Remifentanil versus meperidine (pethidine)

7 randomized-controlled trials comparing remifentanil administered intravenously as a PCA bolus to meperidine administered intramuscularly through a

Table 3. Remifentanil studies evaluating clinical efficacy for labor analgesia in comparison with epidural analgesia.

Reference	Study design	N	Bolus (mcg/kg) or infusion (mcg/kg/min)	Lockout time (min)	Active comparator	Pain score post-intervention (total 100 mm)	Conversion to neuraxial analgesia (N)
Douma[46]	RCT	20	Bolus: 0.5	2	Ropivacaine + sufentanil	R: 40 mm[a] Rop + S: 16 mm	5% (1/20)
Ismail[47]	RCT	1140	Bolus: 0.1–0.9	1	EA: L + F CSE: L + F	R: 34 mm[b] EA: 36 mm CSE: 23 mm	0
Tveit[48]	RCT	39	Bolus: 0.15 + 0.15 mcg/kg increments until relief	2	Ropivacaine + fentanyl	R: 36 mm[c] Rop + F: 16 mm	10.5% (2/19)
Stourac[49]	RCT	24	Bolus: 0.24	3	Bupivacaine + sufentanil	R: 46 mm[c] B + S: 41 mm	0
Volmanen[4]	RCT	45	Bolus: 0.3–0.7	1	Levobupivacaine + fentanyl	R: 73 mm[d] L + F: 52 mm	NR

Notes: [a]Statistically significant difference compared to baseline pain score ($P < 0.05$); epidural analgesia group had significantly larger decrease in pain score compared to remifentanil group (no statistics reported); [b]statistically significant difference between remifentanil and CSE groups ($P < 0.01$) but no significant difference between remifentanil and EA groups; [c]no statistically significant difference; [d]statistically significant difference ($P = 0.009$).
Abbreviations: N, number of patients; RCT, randomized controlled trial; R, remifentanil; Rop, ropivacaine; S, sufentanil; L, levobupivacaine; F, fentanyl; CSE, combined spinal-epidural technique; EA, epidural analgesia; B, bupivacaine; NR, not reported.

Table 4. Summary of reported maternal and neonatal effects of remifentanil.

Reference	Bolus (mcg/kg) or infusion (mcg/kg/min)	Mean total dose (mcg)	Sedation	Number of respiratory desaturation episodes	Apgar scores at 1 and 5 min	Fetal heart rate changes
Blair[22]	Bolus: 0.25–0.5	2241	9.5% (2/21)	23.8% (5/21)	Median 8 and 9	9.5% (2/21)
D'Onofrio[33]	Infusion: 0.025–0.15	NR	4% (8/205)	0%	Median 9 and 9	0%
Volikas[34]	Bolus: 0.5	NR	44% (22/50)	0%	Median 9 and 9	20% (10/50)
Volmanen[35]	Bolus: 0.2–0.8	NR	100% (17/17) mild sedation	59% (10/17)	Median 9 and 9	29% (5/17)
Douma[36]	Bolus: 0.7 Infusion: 0.025	1840	NR	74% (37/50)	Mean 8.9 and 9.9	NR
Evron[37]	Bolus: 0.27–0.93	77600	0	0	0 had <7	7.8% (4/43)
Shahriari[38]	Bolus: 0.35–0.7	NR	5% (1/20)	5% (1/20)	≥ 7 and ≥ 9	NR
Thurlow[39]	Bolus: 0.3	NR	NR	39% (7/18)	NR	NR
Blair[23]	Bolus: 0.5	NR	NR	NR	Median 8 and 9	7% (1/15)
Ng[40]	Bolus: 0.37–0.44	NR	0	0	Median 8 and 9	3% (1/34)
Volikas[24]	Bolus: 0.5	3670	NR	NR	Median 9 and 10	NR
Douma[46]	Bolus: 0.5	2817	10% (1/10)	5% (1/20)	NR	NR
Ismail[47]	Bolus: 0.1–0.9	NR	0	0	NR	NR
Tveit[48]	Bolus: 0.15 + 0.15 mcg/kg increments until relief	NR	65% (11/19)	65% (11/19)	Median 9 and 9	10.5% (2/19)
Stourac[49]	Bolus: 0.24	NR	NR	NR	NR	8.3% (1/12)
Volmanen[4]	Bolus: 0.3–0.7	NR	29% (7/24)	54% (13/24)	Median 9	54% (13/24)
Marwah[56]	Bolus: 0.25 Infusion: 0.025–0.05 mcg/kg/min	NR	2.3% (1/47)	14.9% (7/47)	Median 9 and 9	NR
Volmanen[26]	Bolus: 0.4	NR	Increased scores with remifentanil	0	Median 9 and 9	20% (3/15)

Abbreviations: N, number of patients; NR, not reported.

PCA pump or as a continuous intravenous infusion were included in this review (Table 2).[23,24,36–40] Most studies used a fixed-dose regimen when administering remifentanil, except for 2 studies where the investigators titrated the dose based on the patients' pain scores.[37,38] With the exception of 1 study, remifentanil was associated with a lower mean pain score after 1 hour of labor when compared to meperidine (reduction of 21 to 29 mm).[24,36–40] Compared to the studies that used a fixed dose remifentanil regimen, the studies using a titration strategy based on pain scores reported a larger mean difference in pain scores after 1 hour. Blair and colleagues demonstrated a similar mean pain score after 1 hour of labor for patients receiving either remifentanil or meperidine (64 mm versus 69 mm).[23]

4 studies reported a lower rate of patients requesting to switch to neuraxial analgesia after receiving remifentanil compared to those receiving meperidine (10%–13%)[23,24,36,37] and one study reported a higher rate of 39% for patients receiving remifentanil.[39] There was no significant difference in the rate of spontaneous delivery in any of the studies. Sedation was assessed using a 5-point scale (1 = awake, 2 = drowsy, 3 = rousable to voice, 4 = rousable to touch, 5 = unrousable) for 3 studies[23,36,40] or the Ramsey sedation scale for two studies.[37,38] Two studies did not use a sedation scale for assessment.[24,39] Major limitations from these studies include small sample sizes, variations in dosing regimens, inclusion of patients who declined epidural analgesia (and who therefore may have different pain threshold), exclusion of high-risk

patients (eg, multiple gestation, preterm labor), differences in evaluation of clinical and safety outcomes, insufficient power for safety outcomes, and potential bias with confounding variables.[40]

Remifentanil versus epidural analgesia

Regional analgesia has become a popular method for providing pain relief in labor because of its proven efficacy and safety. When compared to non-epidural methods, epidural analgesia has been shown to be the most effective method of providing pain relief in labor.[41] Traditionally, administration of regional analgesia occurs by injecting a local anesthetic through a catheter into the epidural space. Epidural analgesia can be delivered either by bolus or infusion, often with high concentrations (eg, 0.25% bupivacaine). However, using higher doses for epidural analgesia have resulted in prolonged labor, use of oxytocin augmentation and increased occurrence of instrumental vaginal delivery.[42] These undesirable outcomes were likely due to a motor block that leads to leg weakness, poor mobility, and decreased pelvic muscle tone.[43] To avoid these complications, newer techniques are now commonly employed, including a combination of low concentrations of a local anesthetic and opioid. This allows for effective analgesia while maintaining motor function so that mothers have mobility during labor.[44,45]

Intravenous remifentanil has been compared to various epidural analgesia options for labor pain in 5 randomized controlled trials.[4,46–49] For all studies, the patients in the epidural analgesia group received a combination of an anesthetic (eg, ropivacaine, levobupivacaine, bupivacaine) and fentanyl. For 3 studies, remifentanil was associated with a significantly higher mean pain score after 1 hour of labor when compared to epidural group (difference of 11–24 mm).[4,46,47] However, two studies demonstrated no significant difference in pain scores when patients received remifentanil instead of epidural analgesia.[48,49] The maternal satisfaction scores were comparable for both groups. There was a low rate of conversion to neuraxial analgesia (<11%) in the remifentanil group.[4,46–49] It is evident that epidural analgesia provides superior pain relief, but remifentanil may allow patients to tolerate high pain scores.[4]

There were no significant differences in the incidence in instrumental or spontaneous delivery. Sedation was assessed using a 5-point scale (1 = awake, 2 = drowsy, 3 = rousable to voice, 4 = rousable to touch, 5 = unrousable) for 2 studies,[46,48] a 4-point scale (3 = strong, 2 = moderate, 1 = weak, 0 = none) for 1 study,[4] and the Ramsey sedation scale for 1 study.[47] 1 study did not use a sedation scale for assessment.[49] Significant limitations include non-blinding,[48] small sample size, technical problems leading to small recruitment,[48] strict inclusion criteria (healthy pregnant women),[4,46–49] and a short observation period of 1 hour.[4]

Remifentanil versus combined spinal-epidural analgesia

Another neuraxial analgesia technique is the combined spinal-epidural (CSE) analgesia, where an injection of an analgesic, or local anesthetic, or both, is administered into the intrathecal space before or after the placement of an epidural catheter. Spinal analgesia should not be used as a sole technique for pain relief due to its relatively short duration. Because of the risk of permanent neurological damage, the spinal needle is removed after the initial administration and then further analgesia is provided through the epidural catheter.[50] The advantage of this combined approach includes a faster and reliable onset of action, minimal motor blockade, improved mobilization, and lower maternal and neonatal anesthetic concentrations.[51,52] Thus, CSE has become increasingly popular and is routinely provided at many institutions for labor analgesia.[53,54]

A recent Cochrane systematic review was conducted to investigate the relative effects of CSE when compared to epidural analgesia during labor.[55] This review included 27 randomized, controlled trials that involved 3274 women in total, comparing CSE with traditional and low-dose epidurals. CSE was more favorable over traditional epidurals due to having a faster speed of onset, a decreased need for rescue analgesia, and a lower incidence of urinary retention and rate of instrumental delivery. When compared to low-dose epidurals, there was a slightly faster onset with CSE, but more women complained of pruritus. No difference in ability to mobilize, incidence of maternal hypotension, rate of caesarean birth, or neonatal outcomes were observed. Based on the data, the authors concluded that there appeared to be little difference between CSE and epidural analgesia with

respect to overall maternal satisfaction. Also, the authors suggested the use of low-dose epidurals over traditional epidurals to avoid the significantly higher incidence of urinary retention, rescue interventions, and instrumental deliveries.[55]

Only one trial compared the efficacy and safety of remifentanil to the CSE approach.[47] This study included 1140 healthy women early in labor who requested labor analgesia. They were randomized to receive epidural analgesia, remifentanil, or CSE. The results demonstrated that CSE analgesia had a statistically significant decrease in labor duration (9.7 hours in CSE group versus 10.8 hours in epidural group versus 10.3 hours in remifentanil group, $P < 0.01$), duration of latent phase of first stage (6.6 hours versus 7.8 hours versus 7.7 hours, $P < 0.01$), average VAS pain scores (22.56 mm versus 35.6 mm versus 34.3 mm, $P < 0.01$), and highest maternal overall satisfaction score (3.9 versus 2.8 versus 3.0, $P < 0.01$). However, no differences in side effects or neonatal outcomes were observed between the 3 groups. The investigators determined that CSE analgesia was superior to remifentanil and epidural analgesia for pain relief in early labor, but there was no difference in safety outcomes.

Remifentanil versus fentanyl

1 retrospective study and 1 randomized-controlled trial compared the efficacy of remifentanil to fentanyl for the management of labor pain.[36,56] Marwah and colleagues conducted a 5-year retrospective cohort study where patients either received remifentanil PCA (bolus of 0.25 mcg/kg with lockout interval of 2 minutes) and continuous background infusion (initial rate of 0.025 mcg/kg/min, titrated to 0.05 mcg/kg/min if inadequate analgesia) or fentanyl PCA. 98 women were included in this study. The mean pain scores were similar between the two groups (41 mm in remifentanil group versus 49 mm in fentanyl group, $P = 0.86$), but there was a moderate decrease in pain scores for both groups compared to baseline values. More women from fentanyl group wanted to switch to epidural analgesia (13.7% versus 6.4%, respectively; $P = 0.32$). Transient oxygen desaturation was more common in the remifentanil group (13% versus 2%, respectively; odds ratio, 7.32; 95% confidence interval [CI]: 0.85–63.3). Also, more neonates in the fentanyl group required resuscitation compared with those in the remifentanil group (59% versus 25%, respectively; odds ratio, 4.33; 95% CI: 1.75–10.76). Due to the retrospective nature, some information may have been missing and under-reporting of side effects was possible. Also, the opioid choice was at the discretion of the anesthesiologist, leading to potential selection bias.[56]

The randomized-controlled trial by Douma and colleagues investigated the efficacy and safety of remifentanil and fentanyl, administered through a PCA device.[36] The mean pain scores after 1 hour of labor was lower in the remifentanil group compared to the fentanyl group (45.6 mm versus 59.6 mm, $P < 0.01$). Only 13% of patients receiving remifentanil were switched to epidural analgesia, which was comparable to those receiving fentanyl. Women had a lower chance of spontaneous delivery if they received remifentanil (relative risk [RR] of 0.72; 95% CI: 0.57–0.95 $P = 0.02$) but had no difference in risk of instrumental delivery. Compared to fentanyl, the remifentanil group had a higher risk of oxygen desaturation (RR 1.33; 95% CI: 1.00–1.78, $P = 0.05$).

Remifentanil versus nitrous oxide

Volmanen and colleagues conducted a randomized, double-blind, cross-over study comparing remifentanil and nitrous oxide for labor analgesia.[26] 15 patients were randomized to receive either intravenous remifentanil (PCA bolus of 0.4 mcg/kg with 1 minute lockout times) and intermittent inhaled 50% nitrous oxide. The median decrease in pain score was significantly larger for remifentanil compared to nitrous oxide (1.5 mm in remifentanil group versus 0.5 mm in nitrous oxide group, $P = 0.01$) after 20 minutes of labor. The most common adverse event was oxygen desaturation with remifentanil. There were abnormalities in fetal heart rate were reported in 3 patients (20%) after receiving remifentanil. The major limitations of this study included small sample size, suboptimal administration of remifentanil and nitrous oxide, cautious interpretation of statistical analyses due to use of several interrelated tests, and short observation period of 20 minutes.[26]

Optimal dosing regimen

Research has been conducted on the optimal dosing and mode of administration for remifentanil in the management of labor pain. Remifentanil can be

administered as an intermittent PCA bolus with a lockout interval, and a background infusion can be added if desired. Many of the studies investigating remifentanil for labor analgesia used a unique dosing schedule with 0.5 mcg/kg being the most frequent dose. Most studies reported a wide variation in bolus dosing to achieve patient relief, indicating that a fixed-dose regimen may underestimate or overestimate patient requirements.

Balki and colleagues investigated 2 regimens of intravenous remifentanil PCA along with continuous background infusion for labor analgesia.[57] The initial settings in both groups were established as 0.025 mcg/kg/min for infusion, 0.25 mcg/kg for PCA bolus, and 2 minutes for lockout interval. 20 patients undergoing labor were randomized to receive 1 of 2 remifentanil regimens. 10 patients received a stepwise approach from 0.025 to 0.05, 0.075, and 0.1 mcg/kg/min as required with a constant PCA bolus at 0.25 mcg/kg. The other group received an increase in PCA bolus from 0.25 to 0.5, 0.75, and 1 mcg/kg as necessary while the infusion was kept at 0.025 mcg/kg/min. The primary outcomes included maternal pain and patient satisfaction. While the maternal pain, patient satisfaction, and cumulative dose of remifentanil were similar between groups, the overall incidence of adverse effects was greater in the second group, with a significant increase in drowsiness (30% in first group versus 100% in second group, $P = 0.003$), and a non-significant increase in respiratory depression (94.3% ± 2.6% vs. 92.2% ± 3.8%, $P = 0.19$).[57] The findings suggest that intravenous remifentanil PCA is efficacious at a bolus of 0.25 mcg/kg with a lockout interval of 2 minutes and continuous infusion of 0.025–0.1 mcg/kg/min, with close monitoring for respiratory depression. Providing a stepwise approach may treat the pain more effectively since labor pain is an intermittent physiological pain that increases in frequency and intensity as labor progresses. However, Blair et al reported that a background remifentanil infusion led to no significant difference in pain scores and increased incidence of side effects.[22]

One recent randomized-controlled trial investigated differences in analgesic efficiency, safety, and drug consumption depending on dosing regimen. Jost et al randomly assigned 23 patients to receive either classical dosing regimen or the modified bolus regimen for remifentanil.[58] Both groups received a background infusion of remifentanil with the rate of 0.01 mcg/kg/min and PCA bolus upon request. The lockout periods were set to 1 minute for both regimens. For the classical regimen, the infusion rate and bolus dosage were determined based on regimens deemed safe from previous studies. The initial bolus was given at 0.25 mcg/kg then increased to 0.69 mcg/kg depending on patient response. For the modified bolus regimen, the higher infusion rate and profile and no specific rules for the investigator to modify bolus doses (maximum of 60 mcg). Pain scores were lower in women starting with modified regimen (54 mm in the modified bolus regimen group versus 45 mm in the classical dosing regimen group, $P = 0.005$).[58] For the modified regimen, there were fewer requests for analgesia within the lockout period (31 versus 69, $P = 0.041$) and bolus adjustments (0 versus 25, $P < 0.001$). This study was not double-blinded and the modified regimen had many new features (high infusion rate, delivery time, and infusion profile). Jost et al confirmed no increased incidence in side effects with higher infusion rates with increased pain satisfaction.[58]

Tveit and colleagues conducted a prospective, observational study to investigate the impact of a variable stepwise bolus dosing regimen without background infusion on effective analgesia and maternal and neonatal side effects during the first and second stages of labor.[59] Previous studies focused on the first stage of labor since the utility of opioids during the second stage is unclear. 41 patients received an initials bolus of 0.15 mcg/kg with increases in steps of 0.15 mcg/kg with a 2-minute lockout period. Pain scores were significantly reduced after 1 hour of labor (reduction from 76 mm to 46 mm) and at the end of first (63 mm) and second stages of labor (64 mm). 93% of patients were satisfied with this regimen. Only 1 patient had inadequate pain relief and was switched to epidural analgesia. Maternal sedation was moderate and eleven patients (27%) received supplemental oxygen due to oxygen saturations < 92%. Neonatal data was within normal limits.[59] This study demonstrated that remifentanil can be administered for effective analgesia in both first and second stages of labor.

Safety

A major concern regarding the use of opioids in labor is the risk of serious maternal side effects such

as sedation, oxygen desaturation, nausea, vomiting, and hypoventilation. Most studies have reported that maternal sedation and respiratory depression requiring oxygen supplementation is short in duration and associated with no significant adverse consequences (Table 4). Blair and colleagues observed that 4 out of 21 women demonstrated saturations below 90%, and Volmanen and colleagues showed that 10 out of 17 women experienced saturation below 94%.[22,35] However, 2 other studies determined that remifentanil did not cause desaturation in any of the participants.[33,34] Sedation has been reported with remifentanil (0%–65%),[48] but it was rarely disproportionate (Table 4). Comparative studies with other commonly used agents for labor analgesia help to put this in perspective. Several comparative studies have demonstrated similar incidence of respiratory depression and sedation to meperidine with the exception of one study that demonstrated an increased risk with remifentanil (33% in meperidine group versus 74% in remifentanil group, $P < 0.001$).[36] When compared to epidural analgesia, remifentanil was associated with significantly lower oxygen saturation requiring oxygen supplementation (10%–65%)[46,48] in two studies and increased sedation (65% in remifentanil group versus 10% in epidural group, $P < 0.001$) in one study.[48] The other 3 studies comparing remifentanil to epidural analgesia reported similar incidence in maternal sedation and respiratory depression.[4,47,49] Remifentanil had a similar incidence of respiratory depression to fentanyl but had increased level of sedation with one patient having a score > 1.[56] Compared to nitrous oxide, remifentanil caused increased sedation to a moderate degree and slightly lower oxygen desaturation with one requiring respiratory support.[26] No significant differences in hypotension or bradycardia were determined in any of the studies.

In general, when compared to other agents used for labor analgesia, remifentanil is well tolerated and safe. The major concern is the potential for maternal oxygen desaturation, but the incidence associated with remifentanil is not significantly different from that of other analgesic options. The studies showed that desaturation was transient in nature and easily corrected by a dose reduction or administration of nasal oxygen. Yet, administration of remifentanil should be monitored closely by providing 1-to-1 nursing or midwifery supervision. Also, oxygen saturation monitoring and supplemental oxygen should be readily available if needed.

Another potential concern with remifentanil administration is the occurrence of fetal heart rate abnormalities and neonatal depression. For the studies that reported fetal outcomes, many of the observations were not significant in the remifentanil group compared to other agents used for labor analgesia. However, in all studies, the incidence of fetal heart rate abnormalities was low and often required no intervention. Also, for studies evaluating neonatal depression, the Apgar scores were typically within normal limits after administration of remifentanil. No studies of remifentanil for labor analgesia determined an excess of nonreassuring fetal heart rate changes. 1 study demonstrated a lower incidence of fetal heart rate changes compared to meperidine and better neurobehavioral scores in neonates.[23] No neonate required naloxone after delivery, indicating minimal accumulation of remifentanil in the neonate.

These findings confirm that remifentanil is rapidly metabolized and redistributed in the fetus before being quickly eliminated. Maternal vein and umbilical cord blood samples showed placental transfer concentrations that are clinically insignificant.[34] Only one study has addressed breastfeeding issues and reported that 6.3% of newborns who were exposed to remifentanil during labor had difficulty with breastfeeding.[37] Thus, many studies concluded that remifentanil does not cause significant adverse events in the fetus due to the minimal drug accumulation and rapid elimination. Overall, many studies reported low incidence of adverse events, which may overestimate the adverse effects of remifentanil during labor. The conflicting outcomes reported in the various studies may be due to the different definitions used to define the adverse event (eg, respiratory desaturation defined as oxygen saturation $< 90\%$ versus $<94\%$). Yet, most studies stated that patients experiencing side effects from remifentanil recovered quickly and suffered no long-term consequences. Further research using appropriate methodology to investigate the effects of remifentanil on maternal and neonatal safety is warranted.

Patient Preference

Providing satisfactory analgesia for women undergoing labor is necessary and important for a safe and healthy pregnancy. Many surveys have demonstrated that the

timing and availability of analgesia, independent of the mode or delivery of agent itself, are very important for maternal satisfaction.[1] However, analgesia is only one component of maternal satisfaction during labor. Women include other factors that contribute to their satisfaction including whether personal expectations are met, trust in the obstetric team is established, constant follow-up is achieved, adequate support is provided, and involvement in decisions is given.[60]

While neuraxial analgesia is clearly superior to opioids in providing pain relief during labor, there is a need for opioids when patients have contraindications or exhibit a lack of preference for neuraxial analgesia. With a low number of adverse events reported, remifentanil is a potential agent that can be used as an alternative to neuraxial analgesia. Some studies used satisfactory scale with scores ranging from 0 to 10 (with 10 being the highest level of satisfaction). When using the satisfaction score for comparing remifentanil to meperidine, there were 4 studies demonstrating higher overall maternal satisfaction with remifentanil (3.9 to 8.0).[23,36,37,39,40] For one study using meperidine as the active comparator, patients receiving remifentanil were more satisfied (95% versus 35%, $P < 0.001$).[38] The other study using meperidine did not evaluate maternal satisfaction.[24] Remifentanil had similar patient satisfaction scores compared to epidural analgesia in all 5 studies.[4,46–49] Patients preferred to have remifentanil over nitrous oxide for pain relief (93% versus 6.7%, $P < 0.001$).[26]

Also, there were 8 studies where <20% of patients were switched to neuraxial analgesia, indicating a high maternal satisfaction with remifentanil administration.[22–24,34,36,37,46,48] Measures used to evaluate maternal satisfaction were not consistently defined among studies and often poorly reported. Findings regarding satisfaction should be interpreted cautiously and further research is warranted. Yet, women routinely seem to respond positively to this type of analgesic delivery, based on the available data. Although remifentanil is associated with modest reduction in pain scores, most studies reported high maternal satisfaction, which may mean that even a modest degree of pain relief is clinically relevant.

Place in Therapy

In the absence of any contraindications, epidural analgesia remains the first-line option for women requesting pain relief. Currently, remifentanil does not have an approved indication for administration to the pregnant patient; however, manufacturers are not likely to perform trials due to the cost, and obstetric anesthesiologists use other analgesic drugs that are not approved for use.[61] Based on the available clinical evidence, systemic opioids have a promising role as an alternative to epidural analgesia for the management of labor pain. Like other systemic opioids, remifentanil provides modest labor pain relief that is incomplete and temporary and that is most effective during the early stage of labor. Remifentanil also is accompanied with increased level of sedation. It may not provide effective analgesia in the second stage of analgesia. Despite this temporary relief during labor, many studies showed that majority of patients were satisfied with a modest reduction in pain scores after receiving remifentanil. For patients who prefer more complete analgesia, remifentanil may not be the best option.

Although it is not clear from comparative studies which opioid is the most effective, remifentanil is a reasonable option because of its ideal pharmacokinetics. Remifentanil has a rapid onset and offset, low risk of accumulation due to no active metabolites, and minimal maternal and neonatal adverse effects. Both meperidine and morphine have active metabolites that accumulate in renal failure and can cause serious adverse events like prolonged sedation, respiratory depression, and seizures. Other opioids like fentanyl and remifentanil do not have active metabolites. Due to its ideal pharmacokinetics, remifentanil may become popular; however, further investigations to determine the optimal dosing regimen are needed to balance pain relief and undesirable maternal and neonatal side effects.

The PCA settings used in the existing clinical studies and individual differences in analgesic requirements varied significantly. Because of the variation in pain requirements, using a fixed-dose regimen is not ideal since there is a risk of underestimation leading to inadequate pain relief. Also, overestimation is a concern, since this may lead to unwanted adverse effects such as sedation, respiratory and neonatal depression, and fetal heart rate abnormalities. Some studies demonstrated that a stepwise approach for PCA boluses based on patient pain scores may provide modest analgesia without com-

promising maternal or neonatal safety.[58,59] The role of background infusions to provide more effective analgesia for labor pain is unclear due to the paucity of clinical data. Also, the available data on background infusion is inconsistent.

Due to potential risks reported from various studies, remifentanil administration should be monitored closely by a nurse or midwife and an obstetric anesthesiologist. Oxygen saturation should be monitored continuously throughout the administration. Also, respiratory rate, sedation score, pain score, and fetal heart rate should be monitored frequently (eg, every 30 to 60 minutes).

Currently, there have been no cost-benefit analyses of the management of pain during labor. A recent review describes an analysis that demonstrated no significant difference between the costs with epidural technique (considering catheter needle, anesthetic solutions, and material sterilization) and remifentanil (including infusion pumps, supports, extensors, and mean cost of medication).[62]

Conclusions

Current clinical evidence supports the use of remifentanil for the management of pain during first-stage labor. Compared to meperidine, remifentanil reduces pain scores after 1 hour of labor more significantly with similar side-effect profile. Epidural analgesia has a clear benefit over remifentanil in providing pain relief. Due to very limited evidence, definitive conclusions cannot be made when comparing remifentanil compared to fentanyl and nitrous oxide. Remifentanil is a feasible alternative to neuraxial analgesia in cases where neuraxial analgesia is contraindicated, unavailable, or not preferred by patients. Although remifentanil provides only modest pain relief, it is a popular agent of choice among the majority of women undergoing labor. Due to potential safety concerns, patients receiving remifentanil should be monitored closely for respiratory depression and sedation. Large randomized, controlled trials are needed to clarify maternal and neonatal safety and determine the optimal dosing regimen to provide effective analgesia.

Author Contributions

Conceived and designed the concept: SD. Analyzed the data: SD. Wrote the first draft of the manuscript: SD. Agree with manuscript results and conclusions: SD. Developed the structure and arguments for the paper: SD. Made critical revisions and approved final version: SD. The author reviewed and approved of the final manuscript.

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As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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