Remifentanyl versus fentanyl for intravenous patient-controlled labour analgesia: an observational study

Rémifentanyl versus fentanyl pour l'analgésie intraveineuse contrôlée par les patientes en travail: étude observationnelle

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Abstract

Purpose We undertook a retrospective study to compare the analgesic efficacy and effects on neonatal outcome of administering either remifentanyl or fentanyl intravenous patient-controlled analgesia (IVPCA) during labour.

Methods A five-year retrospective cohort study was undertaken of women with more than 24 weeks of gestation who had received either IVPCA remifentanyl or fentanyl for labour analgesia at Mount Sinai Hospital. The sampling timeframe was from November 2005 to March 2010. The standard IVPCA regimen for the remifentanyl group consisted of a PCA bolus $0.25 \mu\text{g}\cdot\text{kg}^{-1}$ with a lockout interval of two minutes, a four-hour limit of 3 mg, and a background infusion of $0.025\text{--}0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, whereas the standard IVPCA regimen for the fentanyl group consisted of a PCA bolus $25\text{--}50 \mu\text{g}$ with a lockout interval of three to six minutes and a four-hour limit of $1\text{--}1.5 \text{ mg}$. The following data were compared: maternal hourly pain scores (verbal pain score scale 0–10), sedation scores (scale 0–3), adverse effects, and neonatal outcomes. Mixed linear modelling was used to analyze longitudinal data on pain scores over time. The exact Wilcoxon test and the Fisher's exact test were used for other comparisons.

Results Ninety-eight women were studied. There was no significant difference in the model-adjusted pain scores between the two groups ($P = 0.86$). There was a moderate decrease in pain scores in both groups compared with the baseline values. There was no difference in maternal side effects between the two groups, although transient oxygen desaturation was observed more frequently in the remifentanyl group than in the fentanyl group (13% vs 2%, respectively; odds ratio, 7.32; 95% confidence interval [CI], 0.85 to 63.3). A larger number of neonates in the fentanyl group required resuscitation compared with neonates in the remifentanyl group (59% vs 25%, respectively; odds ratio, 4.33; 95% CI, 1.75 to 10.76); adjusted (44% vs 8%, respectively; odds ratio, 8.56; 95% CI, 2.17 to 33.77).

Conclusions Intravenous patient-controlled analgesia with either remifentanyl or fentanyl provides a moderate degree of labour analgesia, whereas transient maternal oxygen desaturation is observed more commonly with remifentanyl. Fentanyl is associated with a higher need for neonatal resuscitation.

Résumé

Objectif Nous avons entrepris une étude rétrospective comparant l'efficacité antalgique et les effets sur le nouveau-né de l'administration intraveineuse de rémifentanyl ou de fentanyl contrôlée par les patientes (ACP-IV), au cours du travail.

Méthodes Cette étude rétrospective de cohorte a porté sur cinq ans; les femmes enceintes de plus de 24 semaines et ayant reçu du rémifentanyl ou du fentanyl par ACP-IV pendant le travail à l'hôpital Mount Sinai ont été incluses. L'étude a porté sur la période comprise entre novembre 2005 et mars 2010. Dans le groupe rémifentanyl, le protocole standard de ACP-IV comportait un bolus d'ACP de $0,25 \mu\text{g}\cdot\text{kg}^{-1}$ avec une période d'interdiction de deux

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minutes, une limite de 3 mg en quatre heures et une perfusion de base de 0,025 à 0,05 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$; le protocole d'ACP-IV pour le groupe fentanyl comportait un bolus d'ACP de 25 à 50 μg avec une période d'interdiction de trois à six minutes et une limite de 1 à 1,5 mg en quatre heures. Les données suivantes ont été comparées: scores de la douleur maternelle à toutes les heures (cotée verbalement sur une échelle de 1 à 10), scores de sédation (échelle de 0 à 3), effets indésirables et effets sur le nouveau-né. Une modélisation linéaire mixte a permis d'analyser les données longitudinales des scores de douleur en fonction du temps. Le test exact de Wilcoxon et le test exact de Fisher ont été utilisés pour les autres comparaisons.

Résultats Quatre-vingt dix-huit femmes ont été incluses dans l'étude. Il n'y a pas eu de différences significatives entre les scores de douleur ajustés par le modèle entre les deux groupes ($P = 0,86$). Il y a eu une baisse modérée des scores de douleur dans les deux groupes par rapport aux valeurs de base. Il n'y a pas eu de différences entre les deux groupes pour les effets indésirables chez les mères bien qu'une désaturation transitoire en oxygène ait été observée plus souvent dans le groupe rémifentanyl que dans le groupe fentanyl (13 % et 2 %, respectivement; rapport de cotes, 7,32; intervalle de confiance à 95 % [IC], 0,85 à 63,3). Un plus grand nombre de nouveau-nés du groupe fentanyl ont nécessité une réanimation comparativement aux nouveau-nés du groupe rémifentanyl (59 % et 25 %, respectivement; rapport de cotes, 4,33; IC à 95 %, 1,75 à 10,76); valeurs ajustées (44 % et 8 %, respectivement; rapport de cotes, 8,56; IC à 95 %, 2,17 à 33,77).

Conclusions L'analgésie intraveineuse au rémifentanyl ou au fentanyl contrôlée par les patientes a procuré un degré modéré d'analgésie, alors qu'une désaturation maternelle en oxygène était observée plus souvent avec le rémifentanyl. Le fentanyl a été associé à un recours plus fréquent à la réanimation néonatale.

There is a well-established need for an effective alternative to regional analgesia for labour, particularly in women with either contraindications or unwillingness to receive epidural analgesia. There are many reasons why a woman may not be a candidate for an epidural placement, including bleeding disorders, spinal abnormalities, neurological disorders, and infections.

Intravenous patient-controlled analgesia (IVPCA) is considered a safe alternative during labour as it allows better titration of the drug. Meperidine was the first opioid to be used for IVPCA for labour; however, the drug has poor efficacy and it is associated with a high incidence of nausea, sedation, and neonatal respiratory depression.¹

Butorphanol, tramadol, nalbuphine, morphine, fentanyl, and remifentanyl have also been used for labour analgesia; however, there is no clear evidence that any one drug is superior to any other.² Fentanyl and remifentanyl are more popular for this indication as their pharmacokinetic and pharmacodynamic characteristics are favourable to meeting the intensity and undulating characteristics of labour pain.

Remifentanyl is a potent, ultra short-acting μ -opioid receptor agonist with a rapid onset of action in 30–60 sec (blood-effect site equilibration 1.2–1.6 min), peak analgesic effect within 2.5 min,^{3,4} and rapid maternal clearance. Its context-sensitive half-time is about three minutes irrespective of its duration of infusion,⁵ and the drug is quickly redistributed and metabolized in the fetus.^{6,7} Fentanyl is also a short-acting synthetic opioid with a rapid onset of action (blood-effect site equilibration 6.4 min), but it exhibits cumulative effect with repeated or prolonged administration due to reuptake from inactive tissue sites, which leads to an increase in its context-sensitive half-time.^{5,8} The elimination half-life in neonates varies from 75 to 440 min.⁹

A randomized controlled trial by Douma *et al.* has compared IVPCA with remifentanyl, fentanyl, and meperidine for labour analgesia.¹⁰ They found differences in the maternal pain scores only during the first hour and no differences in the neonatal outcome between the three groups. To date, the literature supports the safety of remifentanyl from a neonatal standpoint,^{6,7,11–24} while several studies have shown that fentanyl PCA may be associated with neonatal depression.^{1,9,25–28} Therefore further research is needed to ensure the safety of these drugs while used for IVPCA in labouring women. Based on our previous studies,^{15,29} a policy has been implemented at our institution in the last five years for the use of both remifentanyl and fentanyl IVPCA for labour; however, the regimens differ from those reported in the study by Douma *et al.*

The objective of this study was to compare remifentanyl with fentanyl in terms of analgesic efficacy and maternal/neonatal adverse effects of IVPCA for labour analgesia.

Methods

After approval by the Research Ethics Board at Mount Sinai Hospital, we conducted a retrospective chart review of all patients who had received either IVPCA remifentanyl or fentanyl in labour at our institution during November 2005 to March 2010. We reviewed medical and electronic database records of both the mothers and the neonates. Inclusion criteria were women with > 24 weeks of gestation. Exclusion criteria were women receiving IVPCA for termination of pregnancy or those with stillbirths.

The standard IVPCA regimens consisted of: a) remifentanyl PCA (diluted as $50 \mu\text{g}\cdot\text{mL}^{-1}$) demand boluses $0.25 \mu\text{g}\cdot\text{kg}^{-1}$ with a lockout interval of two minutes, a four-hour limit of 3 mg, and a continuous background infusion at the rate of $0.025 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (level 1), which could be increased to $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (level 2) if the analgesia was inadequate; b) fentanyl PCA (diluted as $20 \mu\text{g}\cdot\text{mL}^{-1}$) demand boluses 25–50 μg with a lockout interval of three to six minutes, a four-hour limit of 1–1.5 mg, and without any background infusion. The drugs were administered via the proximal port of an intravenous extension set using the PCA Graseby syringe pump (model 3300, IVAC Medical Systems, Hampshire, UK).

The usual monitoring protocol during the PCA administration consisted of monitoring heart rate (HR), non-invasive blood pressure (BP), respiratory rate, and continuous oxygen saturation (SpO_2) by pulse oximetry as well as monitoring pain and sedation scores. The monitoring was carried out every ten minutes for 30 min after PCA initiation and then every hour until the PCA pump was discontinued. Pain was recorded on a verbal pain score scale (verbal pain score 0–10, where 0 = no pain and 10 = maximum pain), while sedation was recorded on a four-point scale (0–3, where 0 = alert; 1 = mild - drowsy, opens eyes to name; 2 = moderate - drowsy, opens eyes to touch; 3 = severe - somnolent, difficult to arouse).¹³ Oxygen was supplemented to maintain $\text{SpO}_2 > 95\%$ when necessary. Fetal HR and uterine activity were monitored continuously by external tocodynamometer.

In addition to the above data, we recorded the detailed PCA information as well as maternal side effects such as desaturation ($\text{SpO}_2 < 90\%$ and 95%), drowsiness, dizziness, nausea/vomiting, muscle rigidity, respiratory depression, hypotension ($\text{BP} < 90 \text{ mmHg}$ or $< 20\%$ of baseline), bradycardia ($\text{HR} < 50 \text{ beats}\cdot\text{min}^{-1}$), and pruritus. Neonatal data consisted of Apgar scores, analysis of cord blood gases, resuscitation efforts (if any), and any confounding factors that would influence resuscitation, such as general anesthesia, severe congenital anomalies, very low birth weight babies, and meconium aspiration. The data on maternal and neonatal outcome measures were analyzed, and results of the remifentanyl and fentanyl groups were compared.

Statistical analysis

Mixed linear modelling was used to analyze the longitudinal data on pain scores recorded every hour until PCA ended. This approach takes into account the correlation of repeated measurements for each patient, and by using predicted population margins, it allows for valid inferences to be made about the longitudinal treatment effect despite the varying number of women still in labour at any time

point (SAS Institute Inc. 2004, SAS/STAT® 9.1 User's Guide; Cary, NC, USA). The model for the primary analysis of pain included fixed effects for the treatment group baseline pain and a linear term for time (as pain scores will generally increase over the course of labour). To identify differences between the two drug groups, Student's *t* tests were used for continuous variables and Chi square tests were used for categorical variables, unless otherwise noted. In those cases, Wilcoxon Rank-Sum test was used for differences between median ranks for continuous or ordinal variables, and Fisher's exact test was used for categorical data due to small cell sizes. A *P* value of < 0.05 was considered statistically significant.

To determine sample size requirements, we used the methods³⁰ of Frison and Pocock for repeated measure linear models that control for baseline outcome level. We ascertained that it would be necessary to abstract 102 charts (51 charts for each treatment group) to detect a difference of 1.3 cm in verbal pain scores (i.e., a moderate effect size; Cohen's $d = 0.45$) with 80% power. This calculation assumed a two-sided type I error of 0.05, at least two follow-up measurements for each participant, a conservative correlation between baseline and follow-up measurements of 0.5, and a conservative estimate of correlation between follow-up measurements of 0.8. The standard deviation for differences in verbal pain scores was estimated as 2.9 cm from the Douma trial.¹⁰

Results

In our database, we identified 261 patients who received IVPCA during labour, and 98 of these parturients had live infants > 24 weeks of gestation (Fig 1). Forty-seven parturients had received remifentanyl (Group R) IVPCA and 51 had received fentanyl (Group F) IVPCA during labour. Except for a higher mean gestational age of the parturients in Group R compared with those in Group F, the two groups were similar with respect to patient characteristics, type of labour, mode of delivery, and anesthesia used for Cesarean delivery. The cervical dilatation at the start of PCA was similar in both primi- and multigravidas in both groups (Table 1). The most common indication for PCA was epidural refusal followed by coagulation-related issues (Table 2).

Both groups of patients demonstrated an initial reduction in pain scores followed by a gradual increase in pain scores as labour progressed. The overall decrease in pain scores was moderate compared with the baseline values, with a maximum decrease from 7.6 (2.2) cm to 4.1 (3.1) cm in Group R and 8.2 (2.1) cm to 4.9 (3.2) cm in Group F (Table 3). Fig. 2 shows the model-adjusted mean pain scores for both groups at each time point measured, while

Fig. 1 Study flow sheet

Fig. 3 shows the estimated difference between the groups (with 95% confidence interval [CI]) at each time point, taking into account the baseline differences). Overall, pain scores did not differ significantly between groups ($F(1, 33) = 0.03$; $P = 0.86$), and there were no significant differences in pain scores within each group over time ($F(9, 200) = 1.73$; $P = 0.09$). Further, the differences in pain scores (or lack thereof) between the groups were similar at each time point ($F(8, 44) = 0.92$; $P = 0.510$) (Fig. 2). At all times following baseline, the 95% CI for the estimated mean difference covered the null value of “0,” suggesting that there were no differences between the two groups at any point during the study period (Fig. 3). The sedation scores were significantly higher in Group R compared with Group F; however, only one patient in each group had a maximum sedation score > 1 (Table 3).

Ninety percent of patients continued to use PCA until delivery, while only 10% crossed over to epidural analgesia. More women from Group F crossed over to epidural, with an almost double average duration of epidural analgesia until delivery compared with Group R (6:58 (5:15) hr:min vs 3:33 (2:35) hr:min, respectively; Mean Difference, 3:25; 95% CI, 1:46 to 5:04) (Table 4). The duration of PCA use was similar in both groups; however, the

percentage of successful demands was significantly higher in Group R vs Group F (70 (23)% vs 57 (25)%, respectively; Mean Difference: 12.6%; 95% CI, 2.9 to 22.3) (Table 4), suggesting inadequate dosing in Group F despite its longer therapeutic half-life. In Group R, 32% of patients required an increase in the background infusion to level 2, while in Group F, 25% of patients received a higher PCA bolus dose of 50 μ g.

Side effects are summarized in Table 5. There was a higher incidence of desaturation ($SpO_2 < 90\%$) in Group R compared with Group F (13% vs 2%, respectively; odds ratio, 7.32; 95% CI, 0.85 to 63.3). However, the desaturation episodes were transient in all cases and easily reversible by oxygen supplementation or patient arousal.

The neonatal data were analyzed for 88 neonates, and neonates of women who had crossed over to epidural analgesia prior to delivery were excluded. The neonatal weight in Group R was higher than that in Group F; however, in both groups, the neonatal weight was in the average range (2.5–4.5 kg).³¹ In Group F, the percentage of neonates with Apgar scores < 7 at one minute was more than two-fold that in Group R (39% vs 18%, respectively; odds ratio, 2.83; 95% CI, 1.07 to 7.53) as was the percentage of those requiring resuscitation (bag and mask

Table 1 Patient demographics, labour and delivery data

	Remifentanyl Group (<i>n</i> = 47)	Fentanyl Group (<i>n</i> = 51)
Age (yr)	30.9 (6.8)	30.7 (6.5)
Weight (kg)	78.0 (17.6)	82 (33.7)
Height (cm)	163.3 (8.7)	160.9 (13.4)
Body mass index (kg·m ⁻²)	29.2 (6.1)	34.4 (31.0)
Gestational age (weeks)	38.5 (3.0)	36.5 (4.3)
Primipara, <i>n</i> (%)	21 (44.7)	22 (43.1)
Multipara, <i>n</i> (%)	26 (55.3)	29 (56.9)
Labour onset, <i>n</i> (%)		
Spontaneous	38 (80.9)	37 (72.5)
Induced	9 (19.1)	14 (27.5)
Labour augmented	30 (63.8)	30 (58.8)
Cervical dilatation		
Start of PCA (cm)	5 (1, 10)	4 (1, 10)
End of PCA (cm)	10 (2, 10)	10 (2, 10)
Mode of delivery, <i>n</i> (%)		
Spontaneous vaginal	37 (78.7)	44 (86.3)
Cesarean	10 (21.3)	7 (13.7)
Anesthesia for Cesarean delivery, <i>n</i> (%)		
General	4 (40.0)	3 (42.9)
Regional	6 (60.0)	4 (57.1)

Values are expressed as mean (standard deviation) or *n* (%). PCA = patient-controlled analgesia. Regional anesthesia includes spinal, epidural, or combined spinal-epidural anesthesia

Table 2 Indications for intravenous patient-controlled analgesia

Indications	Remifentanyl Group (<i>n</i> = 47)	Fentanyl Group (<i>n</i> = 51)
Epidural refusal	25 (53.2)	26 (51.0)
Epidural failure	2 (4.3)	6 (11.8)
Bleeding/coagulation problems	12 (25.5)	7 (13.7)
Neurological problem	3 (6.4)	1 (2.0)
Spine deformities/surgeries	4 (8.5)	8 (15.7)
Undetermined	1 (2.1)	3 (5.9)

Values are expressed as *n* (%)

ventilation/intubation) (59% vs 25%, respectively; odds ratio, 4.33; 95% CI, 1.75 to 10.76) (Table 6). The adjusted difference in the neonates with the need for resuscitation was also significant (Group F vs Group R: 44% vs 8%; odds ratio, 8.56; 95% CI, 2.17 to 33.77) even when the neonates with confounding variables, such as general anesthesia for Cesarean delivery, congenital anomalies, very low birth weight babies (≤ 1500 g), and those with meconium aspiration, were eliminated from the analysis. The incidence of these confounding variables was similar and not

Table 3 Pain and sedation scores

	Remifentanyl Group (<i>n</i> = 47)	Fentanyl Group (<i>n</i> = 51)	<i>P</i> value*
Pain score, mean (SD)			
Baseline	7.6 (2.2)	8.2 (2.1)	0.17
Minimum	4.1 (3.1)	4.9 (3.2)	0.27
Sedation Score, <i>n</i> (%)			
Maximum			0.001
0	24 (55.8)	35 (87.5)	
1	18 (41.9)	4 (10.0)	
2 or 3	1 (2.3)	1 (2.5)	
Minimum			0.48
0	38 (97.4)	43 (100.0)	
1	1 (2.6)	0 (0.0)	
2 or 3	0 (0.0)	0 (0.0)	

* Wilcoxon Rank-Sum test for verbal pain score scale (0-10; 0 = no pain, 10 = maximum pain). Fisher's exact test for sedation scale (0-3; 0 = alert; 1 = mild - drowsy, opens eyes to name; 2 = moderate - drowsy, opens eyes to touch; 3 = severe - somnolent, difficult to arouse). SD = standard deviation

Fig. 2 Model-adjusted least-square mean pain scores with confidence intervals at each time point stratified by drug group

significantly different between the groups. However, none of the neonates was administered naloxone, and the umbilical cord gases were within normal range and did not differ between the two groups (Table 6). On further data stratification of resuscitated (*n* = 37) vs non-resuscitated neonates (*n* = 51), we found no differences in the maternal length of gestation, total drug requirement, hourly drug consumption, or the duration of PCA between the groups.

Discussion

For management of labour analgesia, we found no difference in the analgesic efficacy of either remifentanyl or

Fig. 3 Estimated differences in mean pain scores between the two groups (Remifentanyl group – Fentanyl group) at each time point with 95% confidence interval. The overall difference in pain scores between the groups was not statistically significant ($P = 0.86$)

fentanyl IVPCA with the regimens administered at our institution. Overall, there was a moderate reduction in pain scores in both groups throughout the duration of labour, though pain scores tended to increase with the progress of labour, especially after five to six hours of drug administration. Similar degrees of analgesia have been shown in other studies; however, most of these studies evaluated analgesic efficacy only for the first two to three hours after initiation of PCA.^{10-14,25} One possible explanation for an increase in pain scores towards the end of labour in our study was the practice of continuing PCA into the second stage of labour when the intensity and frequency of pain are likely to be greater. Douma *et al.*¹⁰ observed superior analgesia with remifentanyl compared with fentanyl in labouring patients; however, the difference was evident only during the first hour of treatment, and pain scores returned to baseline values in both groups within three hours of initiation of PCA. Moreover, in their study, remifentanyl was associated with a higher incidence of sedation and itching, and both drugs produced significant maternal oxygen desaturation. These differences could be attributed to the different PCA regimens used in their study compared with those used in ours. They used a larger PCA bolus dose

Table 5 Side effects

	Remifentanyl Group (<i>n</i> = 47)	Fentanyl Group (<i>n</i> = 51)
Desaturation < 95%	7 (14.9)	6 (11.8)
Desaturation < 90%	6 (12.8)	1 (2.0)
Drowsiness	4 (8.5)	2 (3.9)
Dizziness	3 (6.4)	0 (0.0)
Nausea	3 (6.4)	1 (2.0)
Vomiting	5 (10.6)	4 (7.8)
Pruritus	4 (8.5)	3 (5.9)
Hypotension	1 (2.1)	0 (0.0)
Bradycardia	0 (0.0)	1 (2.0)
Muscle rigidity	0 (0.0)	0 (0.0)
Oxygen supplementation	15 (31.9)	9 (17.6)

Values are expressed as *n* (%)

for remifentanyl without any infusion and a smaller bolus dose for fentanyl. Our regimens for remifentanyl and fentanyl were based on previous studies performed at our hospital that demonstrated effective analgesia with minimal maternal adverse effects.^{15,29}

Although remifentanyl IVPCA has been used widely in the last decade for pain management during labour with^{11,13,15-18} or without background infusion,^{6,12,14,19-21} its most appropriate dosing regimen is still debated. Effective analgesia has been shown in studies that used infusions and escalating dose regimens titrated to individual patient requirements.^{11,15,17} In our previous study, we showed that a regimen with fixed small PCA boluses and a variable infusion rate titrated to effect provides superior analgesia with fewer side effects compared with a regimen with a fixed infusion rate and variable increasing boluses. Furthermore, in the former regimen, the maternal side effects were seen at a higher infusion rate ($> 0.05 \mu\text{g}\cdot\text{kg}^{-1}$), and hence we considered this as our maximum infusion rate along with a demand bolus.¹⁵ Our rationale for the use of this regimen was influenced by the unique pharmacokinetic profile of remifentanyl. Despite its rapid onset, it has a delayed peak analgesic effect of

Table 4 Intravenous patient-controlled analgesia data

	Remifentanyl Group (<i>n</i> = 47)	Fentanyl Group (<i>n</i> = 51)	<i>P</i> value
Duration of PCA (hr:min)	5:18 (4:20)	4:40 (4:42)	0.49
PCA demands/hr	21.6 (23.7)	21.6 (31.7)	0.99
% Successful demands	70 (23)	57.4 (25.2)	0.02
Crossover to epidural, <i>n</i> (%)	3 (6.4)	7 (13.7)	0.32
Duration of epidural in crossovers, (hr:min)	3:33 (2:35)	6:58 (5:15)	< 0.001
Use of opioids prior to PCA, <i>n</i> (%)	6 (12.8)	6 (11.8)	0.88
Total consumption of drug (μg)	1,667 (1,490)	1,216 (1,347)	–
Amount of drug/hr (μg)	374 (235)	226 (122)	–

SD = standard deviation;
Values are expressed as mean (SD) and *n* (%); PCA = patient-controlled analgesia

Table 6 Neonatal outcome data

	Remifentanyl Group (n = 44)	Fentanyl Group (n = 44)
Neonatal weight (g)	3,046.9 (744.3)	2,827.5 (911.6)
Apgar score		
1 min	9.0 (1.0-9.0)	8.0 (1.0-9.0)
5 min	9.0 (2.0-9.0)	9.0 (3.0-9.0)
< 7 at 1 min, n (%)	8 (18.2)	17 (38.6)
< 7 at 5 min, n (%)	3 (6.8)	4 (9.1)
Resuscitation*, n (%)	11 (25.0)	26 (59.1)
Intubation, n (%)	4 (9.1)	9 (20.5)
Neonates with confounding factors [§] , n (%) needing resuscitation	8 (18.2)	12 (27.3)
Very low birth weight	3 (6.8)	6 (13.6)
Congenital anomalies	1 (2.3)	1 (2.3)
GA for Cesarean delivery	3 (6.8)	3 (6.8)
Meconium	3 (6.8)	4 (9.1)
Resuscitation* (excluding confounders [§]), n (%)	3/36 (8.3)	14/32 (43.8)
Intubation (excluding confounders [§]), n (%)	0/36 (0.0)	1/32 (3.13)
Umbilical artery blood gases		
pH	7.3 (0.1)	7.3 (0.1)
pO ₂ (mmHg)	23.1 (9.5)	24.3 (9.0)
pCO ₂ (mmHg)	53.9 (9.3)	53.2 (10.6)
Bicarbonate (mmol·L ⁻¹)	23.2 (2.7)	22.2 (3.9)
O ₂ saturation (%)	0.4 (0.2)	0.5 (0.2)
Base excess (mmol·L ⁻¹)	-4.3 (2.5)	-4.8 (3.3)
Umbilical vein blood gases		
pH	7.3 (0.1)	7.3 (0.1)
pO ₂ (mmHg)	28.5 (8.0)	27.8 (8.1)
pCO ₂ (mmHg)	47.6 (6.5)	48.6 (10.3)
Bicarbonate (mmol·L ⁻¹)	22.2 (2.6)	22.1 (2.3)
O ₂ saturation (%)	0.5 (0.2)	0.6 (0.2)
Base excess (mmol·L ⁻¹)	-4.3 (2.5)	-4.7 (3.0)

Values are expressed as mean (standard deviation), median (range), and n (%).

GA = general anesthesia.

*Resuscitation was considered as oxygen supplementation, positive pressure ventilation, and intubation. [§]Confounding factors were considered as those influencing Apgar scores or resuscitation

approximately 2.5 min after its administration. So even if the bolus is delivered at the beginning of contraction, the peak effect of the drug may not coincide with the peak of the contraction. Moreover, inter- and intra-individual variability in the pattern of uterine contractions may make it difficult to predict the onset of contractions in a timely manner. Therefore, the use of a background infusion appears to be more rational, and small demand boluses may be added for rescuing pain during contractions. In contrast, a fixed bolus technique is appropriate for fentanyl, and a background infusion does not seem to be necessary due to its cumulative effect and prolonged context-sensitive half-time. Despite this, the use of a low-dose background infusion has been described in some studies with no added maternal or neonatal benefits.^{26,27,32}

The major concern associated with IVPCA with opioids is the maternal and neonatal adverse effects. The incidence of maternal desaturation (SpO₂ < 95%) has been shown to be 40-74% after remifentanyl and up to 56% after fentanyl

PCA.^{10,12,15,22,33} The lower rate of maternal desaturation seen in our study, while providing similar analgesic effects, suggests the use of optimum dose regimens in our patients. Furthermore, the desaturation episodes observed in our patients were transient and responded to deep breathing and oxygen supplementation via nasal prongs. Prophylactic oxygen was also given to all parturients receiving level 2 infusion in the remifentanyl group and to some patients in the fentanyl group, which may partially explain the smaller incidence of desaturation in our patients. In their prospective study, D'Onofrio *et al.* found no evidence of desaturation despite using an infusion of remifentanyl 0.025-0.15 µg·kg⁻¹·min⁻¹ in an escalating manner without PCA boluses.¹¹ It is possible that remifentanyl administered as an infusion only is not associated with as much desaturation as its administration in the form of PCA boluses with or without infusions.^{10,12,15,17,33} Nevertheless, continuous pulse oximetry during opioid administration for labour analgesia is warranted regardless of the PCA protocol used.

It was concerning to observe a higher number of neonates in the fentanyl (59%) group than in the remifentanyl (25%) group requiring resuscitation. Although more neonates in the fentanyl group (39%) than in remifentanyl group (18%) had Apgar scores < 7 at one minute, the scores increased significantly at five minutes in most neonates after administration of oxygen and positive pressure ventilation or intubation. Furthermore, no differences were observed in umbilical cord gases. In their retrospective study of fentanyl PCA, Morley-Forster *et al.* observed a 44% incidence of moderately depressed neonates with Apgar scores ≤ 6 at one minute. They found a positive correlation between depressed infants and both total maternal fentanyl dose and the rate of fentanyl consumption.²⁷

Halpern *et al.* compared IVPCA fentanyl with epidural analgesia and reported a higher incidence of active neonatal resuscitation (52%) and naloxone use (17%) in the PCA fentanyl group.²⁸ The use of naloxone in up to 36% of cases has been described to overcome neonatal depression due to PCA fentanyl.²⁶ Naloxone is not used routinely at our institution unless respiratory depression is persistent. Since most neonates improved with resuscitative efforts, naloxone was not administered in any of our neonates. As per the American Heart Association neonatal resuscitation guidelines, the administration of naloxone is not recommended as part of the initial resuscitative efforts in the delivery room for newborns with respiratory depression. Naloxone has a shorter half-life than fentanyl; therefore, the neonate must be monitored closely for recurrent apnea or hypoventilation, and subsequent doses of naloxone may be required.³⁴ Despite the lack of visible neonatal depression at birth, during a 12-hr monitoring period after birth, Nikkola *et al.* observed numerous events of desaturation ($\text{SpO}_2 \leq 90\%$) in neonates of mothers who received fentanyl PCA.²⁵ This indicates the potential for fentanyl—due to its long half-life—to cause delayed respiratory depression in neonates after PCA use.

Our findings of remifentanyl PCA administration on neonatal outcome are in keeping with those from other studies^{13,15,24} and show superior results compared with fentanyl PCA. We found no association between the total dose of opioid or the rate of its consumption and the need for neonatal resuscitation.

The main limitation of our study is its retrospective nature; hence, there is a possibility of some missing information and under-reporting of side effects. However, since we have a standard neonatal resuscitation form and other electronic sources of data verification, we believe that accurate information was recorded. There is a possibility of selection bias as the choice of opioid was at the discretion of the anesthesiologist. However, the bias is likely to be small because the patient demographics were similar between the two groups. Although satisfaction scores—decisive in

evaluating the response to PCA—were not recorded, the fact that 90% of patients continued to use PCA until delivery and only a small number crossed over to epidural analgesia indirectly indicates a high patient satisfaction in both groups.

In conclusion, moderate analgesia without significant maternal side effects was provided with a remifentanyl PCA bolus of $0.25 \mu\text{g}\cdot\text{kg}^{-1}$ with a lockout interval of two minutes and a background infusion of $0.025\text{--}0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and also with a fentanyl PCA bolus of $25\text{--}50 \mu\text{g}$ with a lockout interval of three to six minutes and no background infusion. However, it should be noted that these regimens were used in a tertiary care centre with immediate availability of anesthesia assistance, continuous oxygen saturation monitoring, and one-on-one nursing. Transient maternal drowsiness and desaturation may be seen after remifentanyl, hence oxygen supplementation is recommended while using IVPCA. Given the higher need for resuscitation of the neonates in both groups (more so in the fentanyl group), IVPCA should be considered for labour analgesia only when resuscitation equipment and personnel are immediately available.

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References

1. Rayburn WF, Smith CV, Parriott JE, Woods RE. Randomized comparison of meperidine and fentanyl during labor. *Obstet Gynecol* 1989; 74: 604-6.
2. Ullman R, Smith LA, Burns E, Mori R, Dowswell T. Parenteral opioids for maternal pain relief in labour. *Cochrane Database Syst Rev* 2010; 9: CD007396.
3. Glass PS. Remifentanyl: a new opioid. *J Clin Anesth* 1995; 7: 558-63.
4. Babenco HD, Conard PF, Gross JB. The pharmacodynamic effect of a remifentanyl bolus on ventilatory control. *Anesthesiology* 2000; 92: 393-8.
5. Egan TD, Lemmens HJ, Fiset P, *et al.* The pharmacokinetics of the new short-acting opioid remifentanyl (GI87084B) in healthy adult male volunteers. *Anesthesiology* 1993; 79: 881-92.
6. Volikas I, Butwick A, Wilkinson C, Fleming A, Nicholson G. Maternal and neonatal side-effects of remifentanyl patient-controlled analgesia in labour. *Br J Anaesth* 2005; 95: 504-9.
7. Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanyl: placental transfer, maternal and neonatal effects. *Anesthesiology* 1998; 88: 1467-74.

8. Kapila A, Glass PS, Jacobs JR, et al. Measured context-sensitive half-times of remifentanyl and alfentanil. *Anesthesiology* 1995; 83: 968-75.
9. Koehntop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986; 65: 227-32.
10. Douma MR, Verway RA, Kam-Endtz CE, van der Linden PD, Stienstra R. Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanyl, and fentanyl in labour. *Br J Anaesth* 2010; 104: 209-15.
11. D'Onofrio P, Novelli AM, Mecacci F, Scarselli G. The efficacy and safety of continuous intravenous administration of remifentanyl for birth pain relief: an open study of 205 parturients. *Anesth Analg* 2009; 109: 1922-4.
12. Volmanen P, Akural EI, Raudaskoski T, Alahuhta S. Remifentanyl in obstetric analgesia: a dose-finding study. *Anesth Analg* 2002; 94: 913-7.
13. Balcioglu O, Akin S, Demir S, Aribogan A. Patient-controlled intravenous analgesia with remifentanyl in nulliparous subjects in labor. *Expert Opin Pharmacother* 2007; 8: 3089-96.
14. Blair JM, Dobson GT, Hill DA, McCracken GR, Fee JP. Patient controlled analgesia for labour: a comparison of remifentanyl with pethidine. *Anaesthesia* 2005; 60: 22-7.
15. Balki M, Kasodekar S, Dhumne S, Bernstein P, Carvalho JC. Remifentanyl patient-controlled analgesia for labour: optimizing drug delivery regimens. *Can J Anesth* 2007; 54: 8626-33.
16. Roelants F, De Franceschi E, Veyckemans F, Lavand'homme P. Patient-controlled intravenous analgesia using remifentanyl in the parturient. *Can J Anesth* 2001; 48: 175-8.
17. Blair JM, Hill DA, Fee JP. Patient-controlled analgesia for labour using remifentanyl: a feasibility study. *Br J Anaesth* 2001; 87: 415-20.
18. Owen MD, Poss MJ, Dean LS, Harper MA. Prolonged intravenous remifentanyl infusion for labor analgesia. *Anesth Analg* 2002; 94: 918-9.
19. Olufolabi AJ, Booth JV, Wakeling HG, Glass PS, Penning DH, Reynolds JD. A preliminary investigation of remifentanyl as a labor analgesic. *Anesth Analg* 2000; 91: 606-8.
20. Evron S, Glezerman M, Sadan O, Boaz M, Ezri T. Remifentanyl: a novel systemic analgesic for labor pain. *Anesth Analg* 2005; 100: 233-8.
21. Dhileepan S, Stacey RG. A preliminary investigation of remifentanyl as a labor analgesic. *Anesth Analg* 2001; 92: 1358-9.
22. Thurlow JA, Laxton CH, Dick A, Waterhouse P, Sherman L, Goodman NW. Remifentanyl by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. *Br J Anaesth* 2002; 88: 374-8.
23. Hill D. The use of remifentanyl in obstetrics. *Anesthesiol Clin* 2008; 26: 169-82.
24. Hinova A, Fernando R. Systemic remifentanyl for labor analgesia. *Anesth Analg* 2009; 109: 1925-9.
25. Nikkola EM, Ekblad UU, Kero PO, Alihanka JJ, Salonen MA. Intravenous fentanyl PCA during labour. *Can J Anaesth* 1997; 44: 1248-55.
26. Morley-Forster PK, Reid DW, Vandeberghe H. A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia. *Can J Anesth* 2000; 47: 113-9.
27. Morley-Forster PK, Weberpals J. Neonatal effects of patient-controlled analgesia using fentanyl in labor. *Int J Obstet Anesth* 1998; 7: 103-7.
28. Halpern SH, Muir H, Breen TW, et al. A multicenter randomized controlled trial comparing patient-controlled epidural with intravenous analgesia for pain relief in labor. *Anesth Analg* 2004; 99: 1532-8.
29. Castro C, Tharmaratnam U, Brockhurst N, Tureanu L, Tam K, Windrim R. Patient-controlled analgesia with fentanyl provides effective analgesia for second trimester labour: a randomized controlled study. *Can J Anesth* 2003; 50: 1039-46.
30. Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med* 1992; 11: 1685-704.
31. Birthweight - Low Birthweight, High Birthweight. Available from URL: <http://social.jrank.org/pages/100/Birthweight.html> (accessed May 2011).
32. Rosaeg OP, Kitts JB, Koren G, Byford LJ. Maternal and fetal effects of intravenous patient-controlled fentanyl analgesia during labour in a thrombocytopenic parturient. *Can J Anaesth* 1992; 39: 277-81.
33. Volmanen P, Sarvela J, Akural EI, Raudaskoski T, Korttila K, Alahuhta S. Intravenous remifentanyl vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. *Acta Anaesthesiol Scand* 2008; 52: 249-55.
34. American Heart Association; American Academy of Pediatrics. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: neonatal resuscitation guidelines. *Pediatrics* 2006; 117: e1029-38.