Remifentanil patient-controlled analgesia for labour: optimizing drug delivery regimens

[L'analgésie au rémifentanil contrôlée par le patient pour le travail obstétrical : l'optimisation des régimes d'administration des médicaments]

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Purpose: A pilot study was undertaken to compare the efficacy of two regimens of intravenous patient-controlled analgesia (PCA) with remifentanil for labour analgesia.

Methods: Twenty term parturients requesting labour analgesia were randomized to receive one of two regimens of intravenous remifentanil. The initial settings in both groups consisted of an infusion of 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$, a PCA bolus of 0.25 $\mu g \cdot kg^{-1}$ and a lockout interval of two minutes. In Group A, the infusion was increased in a stepwise manner from 0.025 to 0.05, 0.075 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ as required; the bolus was kept constant at 0.25 $\mu g \cdot kg^{-1}$. In Group B, the bolus was increased from 0.25 to 0.5, 0.75 and 1 $\mu g \cdot kg^{-1}$ as necessary; the infusion was kept constant at 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Maternal pain, satisfaction and sedation scores, remifentanil requirement, and side effects were recorded.

Results: Mean pain and patient satisfaction scores, and cumulative doses of remifentanil were similar in the two groups. The overall incidence of side effects was greater in Group B ($P = 0.0007$), with drowsiness observed in 100% of patients, as compared to 30% in Group A ($P = 0.003$). The minimum oxygen saturation levels were 94.3% ± 2.6% and 92.2% ± 3.8% in Groups A and B respectively ($P = 0.19$).

Conclusions: Although pain and satisfaction scores were similar in both groups, the regimen used in Group A was associated with fewer side effects compared to the Group B dosing regimen. This pilot study suggests that remifentanil intravenous PCA is efficacious for labour analgesia as a bolus of 0.25 $\mu g \cdot kg^{-1}$, with a lockout interval of two minutes and continuous infusion of 0.025–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The potential for respiratory depression mandates close respiratory monitoring. Large-scale trials to evaluate safety issues are warranted.

CAN J ANESTH 2007 / 54: 8 / pp 626–633

Objectif *: Une étude pilote a été entreprise afin de comparer l'efficacité de deux régimes intraveineux d'analgésie contrôlée par le patient (ACP) avec du rémifentanil pour le travail obstétrical.*

Méthode *: Vingt parturientes à terme demandant une analgésie pour le travail ont été randomisées à recevoir l'un de deux régimes de rémifentanil intraveineux. Les réglages de base dans les deux groupes consistaient en une perfusion de 0,025 $\mu g \cdot kg^{-1} \cdot min^{-1}$, un bolus ACP de 0,25 $\mu g \cdot kg^{-1}$ et un intervalle d'interdiction de deux minutes. Dans le groupe A, la perfusion a été augmentée par paliers de 0,025 à 0,05, 0,075 et 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ au besoin ; le bolus a été maintenu constant à 0,25 $\mu g \cdot kg^{-1}$. Dans le groupe B, le bolus a été augmenté de 0,25 à 0,5, 0,75 et 1 $\mu g \cdot kg^{-1}$ au besoin ; la perfusion a été maintenue constante à 0,025 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Les douleurs maternelles, les scores de satisfaction et de sédation, les besoins en rémifentanil et les effets secondaires ont été enregistrés.*

Résultat *: Les scores moyens de douleur et de satisfaction des patientes ainsi que les doses cumulatives de rémifentanil ont atteint des résultats similaires dans les deux groupes. L'incidence totale d'effets secondaires était plus élevée dans le groupe B ($P = 0,007$), avec des cas de somnolence chez 100 % des patientes comparativement à 30 % dans le groupe A ($P = 0,003$). Le minimum de saturation en oxygène était de 94,3 % ± 2,6 % et 92,2 % ± 3,8 % dans les groupes A et B respectivement ($P = 0,19$).*

Conclusion *: Bien que les scores de douleur et de satisfaction étaient similaires dans les deux groupes, le régime utilisé par le groupe A a été associé à moins d'effets secondaires que le régime de dosage du groupe B. Cette étude pilote suggère que l'ACP intraveineuse au rémifentanil est efficace pour l'analgésie pour le travail en bolus de 0,25 $\mu g \cdot kg^{-1}$, avec un intervalle d'interdiction de deux minutes et une perfusion continue de 0,025 – 0,1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Toutefois, un monitorage respiratoire attentif est nécessaire en raison du potentiel de développement de dépressions respiratoires. Des essais à grande échelle pour évaluer les questions d'innocuité sont requis.*

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Source of funding: Institutional.

Accepted for publication March 1, 2007.

Revision accepted May 22, 2007.

ALTHOUGH epidural analgesia is chosen by the majority of parturients when available, it may be contraindicated for some and refused by others. Medical problems such as infections, bleeding disorders, spinal abnormalities and maternal anxiety about the procedure, as well as lack of epidural facilities at some centres, demand an alternative to epidural analgesia for such patients. Several options including hypnosis, acupuncture, entonox, and transcutaneous electrical nerve stimulation have been used for labour analgesia, but the efficacy of these methods is inconsistent and depends heavily upon the parturient's expectations for her labour experience. Worldwide, systemic opioids have been offered as effective alternatives to epidural analgesia, meperidine and fentanyl being the most common. Meperidine is associated with a high incidence of maternal nausea and sedation, as well as many adverse fetal and neonatal effects.[1] The use of intravenous patient controlled analgesia (PCA) with fentanyl has been associated with up to a 44% incidence of moderately depressed neonates with low Apgar scores.[2] Moreover, fentanyl does not always provide adequate pain relief for the intense pain of the late first stage of labour, most likely due to its slow onset of action.[3] A search for a new opioid to overcome these problems has led to the introduction of remifentanil for labour analgesia.[4–6]

Remifentanil has a unique pharmacokinetic profile, with a potent ultra-short μ opioid receptor agonist action. It is a piperidine derivative with the normal opioid configuration, but contains an ester linkage that makes the compound susceptible to metabolism by non-specific esterases in blood and other tissues. In addition, the metabolism of remifentanil is independent of renal and hepatic function. It has rapid onset (time to peak effect 60 to 80 sec) and offset times, irrespective of the duration of administration.[7] The drug's context sensitive half-time is three minutes.[8] Remifentanil rapidly crosses the placenta but is quickly redistributed and metabolized in the fetus.[9,10] There have been no reports of associated increases in neonatal respiratory depression or lower Apgar scores with the use of remifentanil prior to delivery. With these properties, remifentanil appears to be the opioid of choice for labour, since it can be appropriately titrated for administration when analgesia is required for either very brief or prolonged periods, without the concern of prolonged recovery. It therefore resembles the description of an ideal systemic analgesic for use during labour.

Despite several encouraging studies and case reports on remifentanil used for labour analgesia, data are inconclusive regarding its appropriate dosing and mode of administration.[4–6,11–18] The ideal dose regimen of remifentanil for labour pain control remains to be determined. The purpose of this pilot study was to compare two regimens of intravenous remifentanil PCA, along with continuous background infusion, for labour analgesia. We hypothesized that a regimen with changes in the background infusion would differ from one with changes in the bolus dose of remifentanil in regards to analgesic efficacy and safety.

Methods

After obtaining approval from the Research Ethics Board at Mount Sinai Hospital, and written informed consent from the patients, a prospective randomized controlled trial was conducted during the period September 2005 – December 2006. The inclusion criteria were: term pregnancy, ASA I and II patients in active labour, who requested systemic analgesia with or without contraindications to epidural analgesia. Patients with allergy or hypersensitivity to remifentanil, opioid dependence or addiction, consumption of narcotics within 24 hr of the study period, fetal heart rate (FHR) abnormalities, fetal compromise and/or language barrier were excluded from the study.

All patients received an intravenous infusion of remifentanil, with a PCA backup. The patients were randomized, via a computer-generated randomization scheme, into one of the two study groups; Group A - constant PCA boluses with a stepwise increase in the infusion rate; and Group B - constant infusion rate with a stepwise increase in the PCA bolus dose. The group allocation was blinded via sealed envelopes until the time of PCA administration. The patient and the obstetrician, as well as the registered nurse collecting the data, were all blinded to the study group. The group allocation was known only to the anesthesiologist who was making changes to the pump settings when needed.

After admission to the labour and delivery room, an 18G intravenous cannula was established. Lactated Ringer's solution was infused at the rate of 150 $mL \cdot hr^{-1}$ through an IMED infusion pump via an infusion line connected to a 'J-extension' set. This ensured precise administration of remifentanil by preventing backflow of the drug or intravenous fluids. Patients were encouraged to labour in a wedged position to prevent aortocaval compression. Maternal monitoring included non-invasive arterial blood pressure (BP), heart rate (HR) and respiratory rate (RR) every 30 min, and continuous pulse oximetry (SpO_2). Continuous FHR and uterine activity were recorded by using external tocodynamometer monitoring. Fetal invasive monitoring, i.e., scalp electrode or fetal scalp

blood samples, was used as warranted for obstetrical indications. One-on-one nursing was available throughout the use of remifentanil.

At each assessment, the patient was requested to grade the pain experienced during contractions over the preceding 30 min. The pain score was assessed with the verbal numeric rating scale (VNRS) from 0 to 10 (0 = no pain, 10 = worst pain).[19] The VNRS was recorded before commencing analgesia, and then every 30 min after analgesic administration until the delivery of the baby. Patient satisfaction, based on a satisfaction score of 0–10 (0 = no satisfaction and 10 = complete satisfaction), was recorded at the same time intervals. Cervical dilatation, drugs used for the induction/augmentation of labour and the duration of the first and second stage were also recorded. All patients were shown the use of the PCA before starting the study, and were encouraged to press the demand button, either at the beginning of a contraction or whenever a contraction was anticipated, should they feel the need for additional analgesia.

Remifentanil was administered as a 50 $\mu g \cdot mL^{-1}$ solution (3 mg diluted in 60 mL normal saline), via the proximal port of the intravenous extension set, using the PCA Graseby syringe pump model 3300 (IVAC Medical Systems, Hampshire, UK). Initially, all patients received a standard regimen of remifentanil with an infusion of 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a PCA bolus of 0.25 $\mu g \cdot kg^{-1}$. The PCA lockout interval was set at two minutes, and the four-hour limit was 3 mg. As labour progressed and the patients required additional analgesia, they received higher doses of either the infusion (Group A) or the PCA boluses (Group B). In Group A (variable infusion, fixed bolus), the infusion rate was increased stepwise from 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, while the bolus of 0.25 $\mu g \cdot kg^{-1}$ was maintained. In Group B (variable bolus, fixed infusion), the bolus dose was increased stepwise from 0.25 $\mu g \cdot kg^{-1}$ to 0.5 $\mu g \cdot kg^{-1}$, 0.75 $\mu g \cdot kg^{-1}$ and 1 $\mu g \cdot kg^{-1}$, while the infusion rate of 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was kept constant (Table I). This stepwise progression was considered anytime during labour, at the patient's request, if there was either no change or worsening of pain scores. Each step was maintained for at least 15 min before progressing to the subsequent one, and the patient was closely monitored by the attending anesthesiologist during this period. The stepwise increase in the bolus or infusion was stopped, and the previous step restored, if any of the following events occurred: RR < 8 $breaths \cdot min^{-1}$, SpO_2 < 90% for more than 15 sec, maternal HR < $50 \cdot min^{-1}$, FHR < $110 \cdot min^{-1}$, or if the patient was not willing to continue. The PCA pump was discontinued immediately after delivery, and the information was downloaded. The patient could choose to cross over to epidural analgesia at any time during labour, unless there was a contraindication to a regional technique.

TABLE I Remifentanil dose regimens

Step	*Group A* *Variable infusion*		*Group B* *Variable bolus*	
	Bolus $\mu g \cdot kg^{-1}$	*Infusion* $\mu g \cdot kg^{-1} \cdot min^{-1}$	*Bolus* $\mu g \cdot kg^{-1}$	*Infusion* $\mu g \cdot kg^{-1} \cdot min^{-1}$
1	0.25	0.025	0.25	0.025
2	0.25	0.05	0.5	0.025
3	0.25	0.075	0.75	0.025
4	0.25	0.1	1	0.025

The primary outcome variables were maternal pain and desaturation since the objective of the study was to assess both the efficacy and safety of the PCA regimens. The secondary outcome measures included maternal satisfaction, remifentanil requirement, and maternal and fetal/neonatal side effects. The patients were asked, within two hours of delivery, about their overall pain and overall satisfaction with the analgesic regimen during labour. Sedation was assessed by the Modified Observer's Assessment of Alertness/Sedation scale of 0–5 (5 = responds readily to name spoken in normal tone, 4 = lethargic response to name spoken in normal tone, 3 = responds only after name is called loudly or repeatedly, 2 = responds only after mild prodding or shaking, 1 = does not respond to mild prodding or shaking, 0 = does not respond to noxious stimulus).[20] Nausea or vomiting was treated with dimenhydrinate, and diphenhydramine was administered for pruritus. Fetal heart rate tracings were analyzed by an obstetrician (P.B.) who was blinded to the study group. At delivery, Apgar scores were noted at one and five minutes and the umbilical cord blood was obtained for analysis.

Statistical analysis

The sample size of ten patients per treatment group was determined prospectively to give 80% power at a 5% significance level, in order to detect the predicted difference of 2 points in the mean values of the VNRS for pain between the two groups.[5,21] Previous studies have reported a standard deviation of 1.5 for pain scores for women using remifentanil for labour analgesia.[5,9]

Mixed linear modelling was used to analyze the lon-

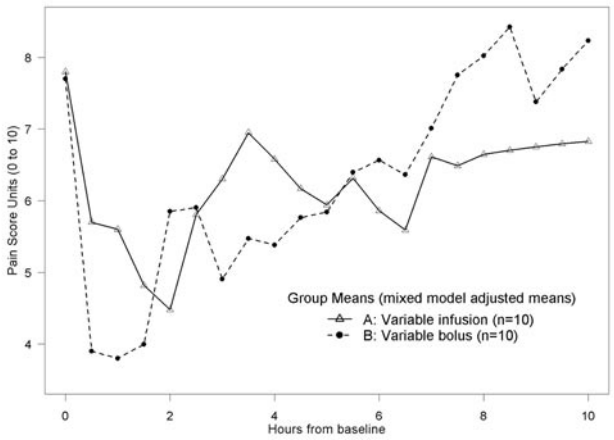

FIGURE 1 Model-adjusted mean pain scores at each time-point in Group A (variable infusion and fixed bolus) and Group B (variable bolus and fixed infusion regimen).

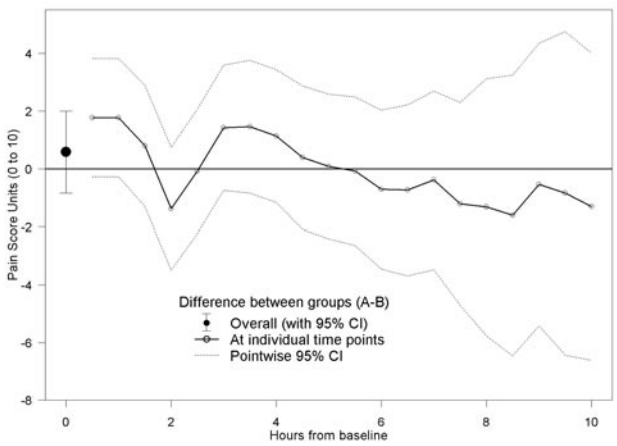

FIGURE 2 Estimated differences in mean pain scores between the two groups (A minus B) at each time-point with 95% confidence interval.

gitudinal data on pain, satisfaction and sedation recorded every 30 min until PCA ended. This approach takes into account the correlation of repeated measurements for each patient, and by using predicted population margins 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 (i.e., A *vs* B), baseline pain, and a linear term for time (as pain scores will generally increase over the course of the labour). Sedation and satisfaction were both modelled with only the treatment group as a fixed effect.

For all other comparisons between groups, the exact Wilcoxon test was used for continuous or ordinal variables, and the Fisher's exact test for categorical data. A *P*-value of < 0.05 was considered statistically significant. Adjustment for multiple comparisons was carried out for the binary side effects using a bootstrap approach with 1 million samples in SAS Proc MULTTEST. In addition, the overall odds ratio (and 95% confidence interval) of the treatment effect was estimated for these binary outcomes using a generalized estimating equations approach (alternating logistic regressions) in SAS Proc GENMOD to account for the association among these outcomes (SAS/STAT® 9.1 User's Guide).

Results

Of 22 parturients screened, 20 were enrolled and completed the study protocol. Ten patients per group, of mixed parity and requesting systemic analgesia, were studied. The indications for systemic analgesia were: epidural refusal (n = 11), on anticoagulants (n = 3), spine surgery (n = 2), failed epidural (n = 1), idiopathic thrombocytopenic purpura (n = 1), Sebastian syndrome (n = 1) and/or neurofibromatosis (n = 1). Both groups were comparable with respect to demographic and obstetric data (Table II).

Figure 1 shows the model-adjusted mean pain scores for both groups at each time-point measured, while Figure 2 shows the estimated difference between the groups (with 95% confidence interval) at each time-point, taking into account baseline differences. The overall model-adjusted difference in pain scores (A minus B) between the groups is not statistically significant ($P = 0.40$); also the confidence interval (-0.84 to +2.00) excludes any differences greater than 2 points on the pain scale (Table III). Similarly, there were no significant differences between groups for each patient's lowest pain or overall pain scores (Table IV).

Satisfaction and sedation data are summarized in Tables III and IV. In both groups, patient satisfaction with analgesia during labour was similar ($P = 0.78$). There was a trend towards higher mean sedation scores ($P = 0.06$) (i.e., less severe sedation), and a significantly higher mean of the lowest sedation score for each patient ($P = 0.01$) in Group A as compared to Group B. One patient in Group B had the lowest sedation score of 2, and responded to mild prodding or shaking in step 2, while all other patients were easily arousable.

TABLE II Demographic, labour and delivery data

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*P-value*
Age (yr)	32.7 ± 5.9	30.4 ± 5.8	0.44
Weight (kg)	85.0 ± 30.0	77.1 ± 14.1	0.96
Height (cm)	162.0 ± 4.9	163.5 ± 10.3	0.99
Primipara	5 (50%)	7 (70%)	0.53
Gestational age (weeks)	39.2 ± 1.5	39.0 ± 1.4	0.98
Labour			
Spontaneous	7 (70%)	8 (80%)	0.83
Induced	3 (30%)	2 (20%)	
Augmented	7 (70%)	3 (30%)	0.14
Cervical dilation			
PCA start (cm)	4.4 ± 1.6	5.4 ± 2.0	0.27
PCA end (cm)	8.8 ± 2.3	9.3 ± 2.2	0.58
Mode of delivery			
Vaginal delivery	6 (60%)	6 (60%)	0.82
Cesarean delivery	4 (40%)	4 (40%)	
Baseline pain (0–10)	7.8 ± 2.6	7.7 ± 2.2	0.86
Baseline sedation (0–5)	5 ± 0	5 ± 0	-

PCA = patient-controlled analgesia. Data expressed as mean ± SD or *n* (%).

TABLE III Summary of longitudinal analysis (mixed linear model) of outcome measures, with group wise means ± SE

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*A - B difference (95% CI)*	*P-value*
Pain	6.09 ± 0.49	5.51 ± 0.46	+0.58 (-0.84, +2.00)	0.40
Satisfaction	8.19 ± 0.44	8.01 ± 0.43	+0.18 (-1.12, +1.48)	0.78
Sedation	4.78 ± 0.16	4.36 ± 0.15	+0.42 (-0.02, +0.87)	0.06

SE = standard error; CI = confidence interval.

Table V shows the mean duration of each step as well as the highest step attained in each group. The requirement of remifentanil and the delivery/demand ratio were similar in both groups (Table V). Only one patient in Group A reverted to an earlier step due to drowsiness and desaturation at step 3. One patient in Group A crossed over to epidural analgesia due to obstetric indications within four hours of commencement of PCA, while all the others continued to use remifentanil until delivery.

The side effects are summarized in Table VI. The joint odds ratio for all of the binary side effects was 6.00 (95% confidence interval: 2.97–13.66, $P = 0.0007$) using Group A (variable infusion) as the control group, so there is strong evidence that in general, the occurrence of side effects was greater in the variable bolus group. The mean lowest SpO_2 levels during PCA use were 94.3% ± 2.6% and 92.2% ± 3.8% in Groups A and B respectively, ($P = 0.19$) [median (range) were 95.5% (89%–97%) and 92.5% (85%–97%) respectively]. The side effects, mainly nausea, vomit-

TABLE IV Additional outcome measures

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*P-value*
Pain score			
Overall pain	5.7 ± 1.4	5.9 ± 1.8	0.74
Lowest pain	3.7 ± 2.4	2.1 ± 2.1	0.13
Satisfaction score			
Overall satisfaction	8.4 ± 1.1	8.6 ± 1.2	0.77
Sedation score			
Lowest sedation	4.4 ± 0.7	3.4 ± 0.7	0.01

Data expressed as mean ± SD.

TABLE V Remifentanil requirement

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*P-value*
Mean duration (hr: min)			
Step 1	2:31	5:03	
Step 2	2:28	2:35	
Step 3	0:58	2:50	
Step 4	0:43	0:00	
Total duration	5:12	7:43	0.21
Highest step, *n* (%)			
Step 1	2 (20%)	3 (30%)	0.46
Step 2	4 (40%)	4 (40%)	
Step 3	2 (20%)	3 (30%)	
Step 4	2 (20%)	0 (0%)	
Remifentanil requirement ($\mu g \cdot hr^{-1}$)	402 (249-624)	474 (188-925)	0.57
PCA demands/hr	17.3 (5.5-32.1)	22.1 (6.3-172.2)	0.46
% Successful demands	75.1 (48-92)	69.7 (12-91)	0.49

PCA = patient-controlled analgesia. Unless specified, data expressed as median (range).

TABLE VI Side effects

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*P-value*
Desaturation < 95%	4 (40%)	6 (60%)	0.42
Desaturation < 90%	1 (10%)	2 (20%)	0.61
Nausea	2 (20%)	6 (60%)	0.095
Vomiting	1 (10%)	4 (40%)	0.17
Drowsiness	3 (30%)	10 (100%)	0.002*
Dizziness	2 (20%)	2 (20%)	0.79
Confusion	0 (0%)	1 (10%)	0.50
Hypotension	0 (0%)	0 (0%)	-
Bradycardia	0 (0%)	0 (0%)	-
Itching	0 (0%)	1 (10%)	0.50

Data expressed as *n* (%). *$P = 0.003$ after adjustment for multiple comparisons.

TABLE VII Fetal and neonatal effects

Parameters	*Group A (n = 10) Variable infusion*	*Group B (n = 10) Variable bolus*	*P-value*
Non-reassuring FHR	1 (10%)	2 (20%)	0.61
Resuscitation	1 (10%)	0 (0%)	0.50
Naloxone requirement	0 (0%)	0 (0%)	-
1 min Apgar score ≥ 7	9 (90%)	10 (100%)	0.50
5 min Apgar score ≥ 7	10 (100%)	10 (100%)	-
Umbilical artery blood gases			
pH	7.25 ± 0.05	7.24 ± 0.08	0.70
pO_2 (mmHg)	23.7 ± 8.1	19.3 ± 7.3	0.32
pCO_2 (mmHg)	51.2 ± 15.0	57.8 ± 9.4	0.30
Base excess ($mmol \cdot L^{-1}$)	-4.6 ± 2.0	-4.3 ± 3.2	0.60
Umbilical vein blood gases			
pH	7.29 ± 0.05	7.27 ± 0.08	0.92
pO_2 (mmHg)	28.2 ± 8.3	26.0 ± 5.3	0.48
pCO_2 (mmHg)	45.5 ± 10.8	51.6 ± 7.7	0.28
Base excess ($mmol \cdot L^{-1}$)	-4.1 ± 2.3	-4.7 ± 3.5	0.91

Data expressed as mean ± SD or *n* (%).

ing, desaturation, drowsiness, confusion and itching, had an equal or lower rate of occurrence in the variable infusion group. Individually, this difference was statistically significant only for drowsiness, which occurred in 3/10 patients in Group A *vs* 10/10 in Group B ($P = 0.002$, $P = 0.003$ after adjusting for multiple comparisons amongst all of the binary side effects). Cardiovascular side effects such as hypotension and bradycardia were not observed in any patient.

There were no differences between groups with respect to fetal and neonatal effects (Table VII). One patient in Group A and two patients in Group B had non-reassuring FHR tracings (either occasional variable/ late decelerations or transient fetal bradycardia) requiring fetal stimulation. One neonate in Group A required resuscitation due to meconium aspiration but was extubated within several seconds. None of the neonates had respiratory depression or required naloxone. The umbilical cord blood gases were within normal range in all neonates.

Discussion

The challenge with any technique of labour analgesia is to provide adequate pain control while minimizing the associated maternal and fetal adverse effects. Labour pain is a unique type of intermittent physiological pain, increasing in frequency and intensity as labour progresses, followed by a significant reduction after the delivery of the infant. To match this pain pattern, considering the exclusive characteristics of remifentanil, this pilot study provided stepwise increments of the drug regimen rather than one standard dose. In addition, there is also variability in the pattern of uterine contractions among labouring patients as well as within each individual patient. Currently, there is no drug with those characteristics that enable the peak effect to coincide with the peak of the contraction. Therefore, it is unlikely that the sole use of PCA bolusing will achieve optimal analgesia for labour. Owing to the fast onset of remifentanil within 60–80 sec, the timely demand of the PCA bolus may coincide with the contraction peak, although this may not be completely reliable. Therefore, we chose a continuous background infusion of remifentanil in both groups to provide constant baseline analgesia, so that only the contraction peaks required treatment with rescue boluses.

Previous studies have used PCA boluses ranging from 0.2 to 1 $\mu g \cdot kg^{-1}$ with a variable lockout interval.[4,12,16,17] However, these studies were associated with incomplete analgesia, a high rate of crossover to epidural analgesia, and side effects such as maternal desaturation, sedation and pruritus. Furthermore, most of the studies did not test remifentanil in the second stage of labour, when the intensity and frequency of pain are likely to be greater.

Roelants et al.[15] reported the use of a low dose infusion (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of remifentanil in addition to PCA boluses (25 μg), with a lockout interval of five minutes, in a case series of six patients. While all their patients benefited from remifentanil PCA, a detailed assessment of the pain and side effects during labour was not undertaken. Although their study indicates the usefulness of background infusion, it did not provide an optimum dose regimen of remifentanil for labouring women because there was no comparison of different bolus doses or infusions. Our study is the first to specifically examine the efficacy of remifentanil PCA for labour analgesia using different boluses and background infusion regimens.

The success of our technique is demonstrated by the high patient satisfaction, with scores ranging from seven to ten in all patients. In addition, 95% of the patients in our study continued to use remifentanil until delivery, declining the offer of an epidural. All women demonstrated an initial decrease in pain scores during the first two hours of remifentanil administration, followed by an increase to a level lower than the baseline throughout the labouring period. This pattern of pain scoring with remifentanil has been demonstrated previously.[6,9,17] Thus, it is interesting to observe the high satisfaction scores despite relatively high pain scores. Such pain scores have also been reported in other studies, and were acceptable to our patients.[4,5,9,17] The discrepancy between pain and

satisfaction scores could reflect the high motivation of patients to receive intravenous analgesia, or perhaps an altered pain perception induced by remifentanil. Our results also suggest that labour pain is not an independent entity, but rather, is influenced by patient expectations and previous experiences, as well as the analgesic technique.

The major concern associated with remifentanil PCA in previous studies is maternal side effects.[13,14,17] The increased incidence of side effects in Group B (variable bolus) observed in our study could possibly have been due to the sudden increases in peak blood concentrations of remifentanil in response to the bolus dose. The incidence of drowsiness was significantly higher in Group B as compared to Group A, and was seen to occur with higher step changes in the PCA bolus doses. One patient in Group B had excessive sedation, requiring mild prodding and shaking for arousal, which was concerning. However, the short duration of action and the lack of cumulation of remifentanil should result in rapid spontaneous resolution of any occurrences of over-sedation. The desaturation episodes observed in our patients were transient and responded to deep breathing and oxygen supplementation via nasal prongs. Desaturation was noted to occur commonly with increasing drowsiness. Desaturation during labour, with or without opioid use, is not uncommon.[4,13,16,17] The data from our study suggest that continuous pulse oximetry during opioid PCA administration for labour analgesia is warranted.

Non-reassuring FHR tracings observed in three patients were short-lived and appeared to be related to obstetric causes rather than remifentanil. Our findings of an absence of any fetal or neonatal adverse effects are consistent with other studies in the literature.[4,5,17] Continuation of remifentanil until the time of delivery produced no observable adverse effects on the neonate.

The primary limitation of this pilot study is the sample size. While the outcome used to determine sample size (pain) was one of the primary outcomes, the other primary outcome (minimum SpO_2 level) and the secondary outcomes were not considered prospectively in the sample size calculation. While ten patients per group provided sufficient statistical power to exclude differences between groups exceeding 2 points on the 0–10 pain scale, we caution that this pilot study was not powered to address safety from the perspective of maternal oxygen desaturations. Based on the demonstrated efficacy of remifentanil for labour analgesia in parturients for whom epidural analgesia is either not feasible or contraindicated, the data from this pilot study warrant large-scale randomized controlled trials to further address patient safety issues.

In conclusion, the appropriate remifentanil regimen is crucial for its success in labour analgesia in order to balance both pain control and side effects. This pilot study suggests that remifentanil be used as a continuous infusion, with a limited bolus dose as a rescue for the peak of contractions. We advocate the regimen of increasing the background infusion ranging from 0.025–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, along with a PCA bolus of 0.25 $\mu g \cdot kg^{-1}$ and a lockout interval of two minutes. We further recommend continuous oxygen saturation monitoring, one-on-one nursing, and the use of supplemental oxygen if the oxygen saturation falls below 95%. Further studies in a large population of patients are warranted to ensure the safety of this regimen.

Acknowledgement

The authors acknowledge Robert Parkes (Biostatistician) for his expert statistical advice, and Leda Ivic Weiss (Research Assistant) for organizing the database and providing basic statistical assistance.

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