Patient-controlled analgesia for labour using remifentanil: 
a feasibility study

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We have investigated the efficacy and safety of remifentanil in a patient-controlled analgesia device for labour in 21 women. Remifentanil was available in increasing doses (bolus doses 0.25–1.0 µg kg⁻¹) with and without a background infusion (0.025–0.05 µg kg⁻¹ min⁻¹). A lock-out time of 2 min was used. Thirteen out of 21 (62%) women chose to continue using remifentanil up to and during delivery. Nineteen out of 21 (90%) achieved a reduction in pain score from baseline. Using a VAS of 0–10 cm the median maximum reduction in pain score was 3 cm (range 0–8 cm). There was a significant reduction (P<0.05) from baseline pain scores (median= 8 cm) to scores at bolus doses in the range 0.25–0.5 µg kg⁻¹ (median=5 cm). There were no significant reductions in the fetal heart rate. Apgar scores and cord blood gas analyses remained within normal limits. We conclude that a remifentanil patient-controlled analgesia system (bolus doses 0.25–0.5 µg kg⁻¹, without a background infusion) may safely provide worthwhile, although incomplete, analgesia for labour.

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There is a need for an effective alternative to epidural analgesia in labour. Over 50% of women either choose not to have, or are unable to have, an epidural yet the only options for analgesia remain entonox. Transcutaneous Electrical Nerve Stimulation (TENS), intramuscular opioids such as pethidine, or alternative techniques, for example relaxation therapy, water bath, and aromatherapy. Entonox and pethidine are not without problems¹ and are of limited efficacy.

The use of pethidine as an analgesic for labour has recently been criticized.² This work demonstrated that pethidine acts as a sedative and not primarily as an analgesic. The timing of maternal injection is also a limiting factor as prolonged fetal depression is a well-documented side effect.³ ⁴

Many women find that nitrous oxide is an unsatisfactory analgesic for established labour⁵ and some are unable to use it effectively because of induced nausea and vomiting. Nitrous oxide may pose a risk to personnel working in areas where it is used for long periods of time without adequate scavenging facilities⁶ ⁷ and nitrous oxide emissions may be implicated in the ‘green-house’ effect.⁸ ⁹ There are increasing calls for the use of nitrous oxide to be reduced, or even abolished, in anaesthetic practice. Before remifentanil was available, no other analgesic had as rapid onset and termination of effect as nitrous oxide. Remifentanil may, therefore, have a unique role to play in obstetric practice where these characteristics are useful.

Remifentanil is a novel, ultra short-acting esterase metabolized synthetic opioid. It is a selective mu opioid agonist and has an ester linkage rendering it susceptible to rapid metabolism by non-specific blood and tissue esterases. Adult pharmacokinetic studies have shown a rapid onset of peak effect (blood–brain equilibration time: 1.2–1.4 min), a short duration of action independent of the duration of infusion (context sensitive half time: 3 min) and rapid clearance (40 ml kg⁻¹ min⁻¹).¹⁰ ¹²

These characteristics may make remifentanil a suitable drug for use in a patient-controlled analgesia system (PCA), with or without a background infusion, for analgesia in labour where severe pain occurs at intervals and rapid recovery between contractions and after delivery is desirable. The purpose of this study was to assess the feasibility of PCA remifentanil as an effective and safe alternative to epidural analgesia in labour.

The safety of remifentanil in obstetric patients and neonates has already been established by Kan and colleagues.¹³ They used an i.v. infusion of remifentanil during
Caesarean section under epidural anaesthesia in a series of 19 patients. This study showed that placental transfer of remifentanil does occur but that it appears to be `rapidly metabolized, redistributed, or both'. This study used a relatively high rate of infusion (0.1 μg kg\(^{-1}\) min\(^{-1}\)) but found there were no adverse effects on neonates. Mild maternal sedation and respiratory depression were noted but responded rapidly to a decrease in infusion rate. Remifentanil has also been used for post-operative analgesia in neonates and has been found to have a similar pharmacological profile in neonates to that of older children and adults.\(^{14}\)

Remifentanil has been used extensively in awake non-obstetric patients as an infusion to supplement a regional technique or in the post-operative period.\(^{15,16}\) Infusion rates of 0.05–0.1 μg kg\(^{-1}\) min\(^{-1}\) have been shown to provide satisfactory pain relief with any respiratory depression responding to small reductions in infusion rate.

There have been several case reports of remifentanil being used in a PCA device for labour in cases of thrombocytopenia,\(^{17,18}\) but this is the first formal evaluation of the feasibility of using a remifentanil PCA device, with or without a background infusion, for analgesia in normal labour.

**Methods**

After obtaining local Research Ethics Committee approval, 21 women (six nulliparous; 15 multiparous), ASA I or II, in established labour with the cervix at a minimum of 3 cm, were studied. Informed written consent was obtained. Patients that had already received pethidine or had requested an epidural were not studied. Other exclusions were twin pregnancy, pre-eclampsia, allergy to any agent under investigation, or failure to obtain informed consent. All patients were aware that remifentanil had not been used for this purpose before and were given a detailed information sheet.

All women had an i.v. cannula inserted (minimum 18-gauge) and i.v. fluids erected to run at 70 ml h\(^{-1}\). A 20-gauge i.v. cannula was also inserted for the remifentanil PCA device. Non-invasive arterial pressure monitoring and pulse-oximetry were established and baseline arterial pressure, heart rate, \(S_aO_2\), respiratory rate, and fetal heart rate were recorded. Contractions were assessed using a Visual Analogue Scale (VAS) for pain. Each woman was asked to record the pain of her contractions on a VAS and also the smallest reduction in that pain which she considered to be worthwhile. The women then discontinued using entonox or TENS if appropriate. All women were aware that they could change to a regional technique at any time if they wished. All were shown how to use the PCA before starting the study and were instructed to press the button either as soon as they felt a contraction beginning or, in the case of those women having frequent regular contractions, whenever a contraction was anticipated. The bolus dose available from the PCA was increased in a stepwise manner and the effect of each dose was assessed after it had been used for 15 min.

There were three ‘levels’ in this study as shown in Figure 1. The patient progressed from level 1 to level 2 and finally to level 3. This progression was continued until either effective pain relief was reached or an adverse effect occurred. Each bolus dose at each level was available for 15 min. The PCA ‘lock-out’ time was initially set at 3 min. The first patient to be studied contracted at a rate of one contraction every 2 min and the 3 min lockout was, therefore, too long. The lockout time was subsequently reduced to 2 min. This 2 min lockout was, therefore, used in all remaining 20 patients. Levels 2 and 3 included a remifentanil infusion as shown. Arterial pressure, heart rate, \(S_aO_2\), respiratory rate, and fetal heart rate were recorded every 5 min.

After each 15 min period, the patient was asked to record the level of pain experienced during the preceding contractions on a VAS (the baseline VAS was not made available to the patient). Nausea, anxiety, sedation, and satisfaction...
scores were also recorded by the patient on a VAS. Any vomiting, dizziness, itching, or muscle stiffness was noted. Sedation was also recorded by the investigator using a score 1–5 (1=awake; 2=drowsy; 3=rousable to voice; 4=rousable to touch; 5=unrousable).

The stepwise increase in dose was stopped in the following circumstances: respiratory rate less than 8/min; $\overline{S_{\text{a}O_2}}$ less than 90% for more than 15 s; mean arterial pressure decreased by more than 25% from baseline; heart rate less than 50 beat min$^{-1}$; fetal heart rate less than 110 beats min$^{-1}$; the patient was comfortable during contractions (VAS 3 or less); the patient was unwilling to continue.

The dose at which the patient reached the VAS that corresponded with ‘the smallest reduction in pain that she considered to be worthwhile’ was noted. The maximum safe dose, for example the dose before developing an adverse effect, was recorded if applicable. If analgesia was inadequate at the end of the study period the patient was allowed to continue to use that dose for the remainder of labour. The investigating anaesthetist and the attending midwife were continuously present in the delivery room whilst the remifentanil PCA was being used.

At delivery, Apgar scores were noted at 1 and 5 min and cord blood was taken for blood gas analysis in every case. All women were asked for their comments about the PCA on the day after delivery. They were asked what they liked, what they disliked and for an overall comment.

Statistics

Parametric data were analysed by repeated measures ANOVA and simple summary statistics and non-parametric scores and scales were analysed by Friedman non-parametric repeated measures test.

Results

Out of 21 who started the study, 13 women (62%) continued to use the remifentanil PCA until delivery. The majority of these were multiparous patients (11 out of 13) and all 13 women had a normal delivery. Of the remaining eight women, four decided to change to a regional technique during the first stage of labour (one of these later required Caesarean section), one decided to change to a regional technique during a prolonged second stage (eventual forceps delivery) and three required a regional technique for delivery. One of these three requested spinal anaesthesia for a ventouse delivery and the remaining two women required a Caesarean section for failure to progress whilst using the remifentanil PCA. The mean (sd) age was 29 (7) yr and the mean (sd) weight was 78 (12) kg. The median (range) cervical dilatation reached before the PCA was started was 3 (3–6) cm.

A reduction in pain score from baseline was achieved in 19 out of 21 women (90%). Analgesia was, therefore, completely unsuccessful in two patients, one of whom was the first patient recruited to the study. The median maximum reduction in pain score achieved was 3 cm (range 0–8 cm) and in 17 out of 21 women (81%) this maximum reduction occurred at the level 1 dose range. Seven women (33.3%) achieved a reduction in pain score to VAS 3 cm and this occurred in all cases at the level 1 dose range. Ten women (48%) achieved the reduction in pain score that they had stated would be worthwhile and again this occurred in every case at the level 1 dose range.

The median pain score at baseline was 8 cm (range 3–10). When the baseline scores were compared with the lowest pain scores recorded at L1B1, bolus 0.25 µg kg$^{-1}$ (median 5 cm), and at L1B2, bolus 0.5 µg kg$^{-1}$ (median 5 cm), a significant reduction in pain scores was found ($P<0.05$). However, increasing the dose to the level 2 dose range (Fig. 1) did not result in any further significant reduction in pain scores. Thirteen women delivered using remifentanil and the median pain score at delivery was 8 cm (range 4–10 cm) (Table 1).

Maximum sedation (VAS) scores were significantly higher at L1B2, bolus 0.5 µg kg$^{-1}$, than at baseline ($P<0.01$). The observer sedation scores (1–5) were also significantly higher at L1B2, bolus 0.5 µg kg$^{-1}$ (median score 2), than those at baseline (median score 1) ($P<0.05$). However, anxiety VAS scores were significantly reduced at L1B2 compared with baseline ($P<0.05$) and satisfaction VAS scores were significantly higher at L1B2 than at baseline ($P<0.01$) (Table 2). There was no significant increase in nausea VAS scores at L1B1 or L1B2 compared with baseline. Heart rate, systolic arterial pressure, and fetal heart rate did not change significantly at doses L1B1 or L1B2 compared with baseline.

Respiratory rate was significantly lower at L1B1, bolus 0.25 µg kg$^{-1}$, and L1B2, bolus 0.5 µg kg$^{-1}$ than at baseline ($P<0.001$). The lowest respiratory rate recorded at the level 1 dose range was 10 breaths min$^{-1}$ and the lowest rate
recorded at any dose was 8 breaths min\(^{-1}\). None of the parturients required naloxone.

Six women experienced an adverse event as predetermined in the procedure; four women had oxygen saturations of <90% for more than 15 s, one had a sedation score of >3 and one had both a sedation score of >3 and an oxygen saturation of <90% for more than 15 s. These adverse events were all transient, responded rapidly to a reduction in dose and occurred at doses greater than level 1 (L2B2-L3B3) (Fig. 1). Vomiting occurred in 10/21 (48%) women, itch in 12/21 (57%) and dizziness in 9/21 (43%) at some point during the study. No muscle stiffness was noted. The mean total dose of remifentanil used was 2241 \(\mu\)g (range 340–6120 \(\mu\)g). Median Apgar scores at 1 and 5 min were 8 (range 5–9) and 9 (range 8–10), respectively, and the mean cord pH was 7.34 (range 7.24–7.43). No baby required naloxone to establish spontaneous respiration. One baby was given naloxone in addition to oxygen but began effective breathing instantly after the injection and it was considered unlikely that the naloxone had been necessary in that case. A fetal heart rate below 110 beats min\(^{-1}\) occurred on two occasions only. In one case, there was a rapid labour and delivery and the fetal heart rate fell transiently to 96 beats min\(^{-1}\) just before delivery. In the second case there was also a rapid labour and delivery and the fetal heart rate repeatedly dipped to below 110 beats min\(^{-1}\) during contractions in the short second stage. In both these cases, the impression was that these findings were probably secondary to the nature of the delivery. The heart rate immediately after delivery in both these cases returned to normal.

The women’s comments on the day after delivery about the PCA are summarized in Table 3.

### Table 3

<table>
<thead>
<tr>
<th>Study number</th>
<th>Parity</th>
<th>Mode of patient of delivery (ND=normal delivery)</th>
<th>Patient comments on day after delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>ND</td>
<td>(Patient changed to epidural as lockout too long)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>ND</td>
<td>Remifentanil was better than entonox</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>ND</td>
<td>No comments recorded</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>ND</td>
<td>No comments recorded</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>Ventouse</td>
<td>Good for most of labour but not for later when pushing</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>ND</td>
<td>Would use again. Did feel drowsy but would not consider that a fault</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>ND</td>
<td>Did not like the way it made me feel. Epidural was much better</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>Caesarean</td>
<td>Great to control yourself. Instant effect when dose was increased</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>ND</td>
<td>Better than pethidine that I used with my first baby</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>ND</td>
<td>Better than pethidine. I felt more in control</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>Caesarean</td>
<td>Good for early labour but then I needed more pain relief and did not want to increase the remifentanil as it made me feel ‘funny’</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>Caesarean</td>
<td>Felt in control and more clear headed than with pethidine. Excellent pain relief (sometimes I did not press the PCA to prove to myself that the pain was still there)</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>ND</td>
<td>Would use again. I felt in control. I did feel drowsy but this helped relaxation between contractions</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>ND</td>
<td>Better than pethidine. I liked being in control. It was difficult to co-ordinate pressing the PCA during pushing</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>ND</td>
<td>Better than pethidine. I felt in control and clear headed after delivery</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>ND</td>
<td>Better than pethidine. I felt more in control during labour and more alert afterwards. It was not good for pain relief for second stage but I would use it again</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>ND</td>
<td>Good until 8–9 cm, then only slight relief with each press. I felt less sleepy than with pethidine</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>ND</td>
<td>No comments recorded</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>ND</td>
<td>Very good, I would recommend it</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>ND</td>
<td>Good for early labour. I opted for epidural as I was making slow progress</td>
</tr>
</tbody>
</table>
| 21           | 0      | Forceps                                       | Good until 9–10 cm. I had a long second stage and found it hard to cope with the pain and, therefore, opted for a spinal

### Table 2

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline (cm)</th>
<th>L1B1 bolus 0.25 (\mu)g kg(^{-1}) (cm)</th>
<th>L1B2 bolus 0.5 (\mu)g kg(^{-1}) (cm)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation VAS maximum score</td>
<td>2 (0–8)</td>
<td>4 (0–9.5)</td>
<td>6 (2–9.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Satisfaction VAS maximum score</td>
<td>4.5 (0–8)</td>
<td>7 (2–9)</td>
<td>8 (2–10)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anxiety VAS minimum score</td>
<td>3 (0–9)</td>
<td>2 (0–5)</td>
<td>2 (0–4)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Discussion

In our study, PCA of remifentanil, without a background infusion and at bolus doses of up to 0.5 \(\mu\)g kg\(^{-1}\) (level 1 dose range) was safe in women in established labour. This dose
Remifentanil PCA for labour

Remifentanil has a unique metabolism by non-specific esterases which results in reduced pharmacokinetic variability and an extremely rapid clearance and offset of effect that is independent of excretory organ function or duration of use. This flexibility and lack of cumulating suggests that remifentanil has advantages over other methods in situations requiring intermittent relief followed by rapid recovery, such as labour. Some problems remain, notably the 90 s delay to peak drug effect and the usual mu agonist side effects.

We set out to investigate whether remifentanil could provide safe and useful analgesia for labour when given in a PCA system. The use of bolus doses of remifentanil in awake patients is controversial with some questioning the technique in patients whose airway is unsecured. Although muscle rigidity has been highlighted as a potential problem, when bolus doses of remifentanil were compared with equipotent doses of alfentanil the incidence and severity of this complication were similar. It is worth noting that doses of remifentanil less than 2 μg kg⁻¹ given over 1 min have not been reported to cause muscle rigidity. Bolus doses as high as 1 μg kg⁻¹ have been used in awake patients. In our study, none of our patients showed evidence of muscle rigidity or serious respiratory depression and, in our judgement, remifentanil PCA (0.05 μg kg⁻¹ boluses) did not increase the risk of regurgitation and aspiration.

Since our study began there have been two case reports of remifentanil used in a PCA system for labour. One reported a 2 min lockout time with bolus doses ranging from remifentanil 35–75 μg. Interesting, the remifentanil was purposefully discontinued in each of the three women when the second stage began. The second report used a much smaller bolus dose (20 μg) and a longer lockout time (3 min). Both reports concluded that remifentanil provided good analgesia for labour.

It was necessary to instruct the parturients in the use of the PCA system. The majority of women readily understood this as similar instruction is given for the use of entonox. Occasionally, analgesia was such that the women were only aware of the peak of the contractions and pressed the button too late. In most of these cases, the assistance of the midwife was invaluable in informing the woman that a contraction was starting.

The assessment of pain relief in labour is not straightforward. The pain experienced is not constant so that what is recorded as the ‘worst pain imaginable’ (10 cm on a VAS) by a woman in early labour may in fact be less severe than that recorded at 8 cm on a VAS at a later stage. Early retrospective assessment of labour pain (2 h post-delivery) considered with the duration of labour may help solve these difficulties. However, in order to assess the efficacy and safety of increasing doses of remifentanil, we recorded VAS scores for pain every 15 min during remifentanil use.

Nineteen women (90%) achieved a reduction in pain score. These were meaningful reductions as even a 1 cm change in VAS score is considered to be clinically significant by patients. Pain scores, as expected, tended to increase as labour progressed. Perhaps the best measure of satisfaction with remifentanil as an analgesic was the number of women who chose to continue to use the remifentanil up until delivery. All women were aware that they could change to an epidural and were encouraged to do so if their pain scores rose significantly as labour progressed.

The bolus dose range that provides effective analgesia in labour was clearly demonstrated by our study. Bolus doses at 0.25–0.5 μg kg⁻¹ without a background infusion (the level 1 dose range) were responsible for the maximum reduction in pain score in 17/21 women. All women recording either a pain score of 3 or less, or those recording the reduction in pain score that they thought to be worthwhile, also did so at the level 1 dose range. Analysis of pain scores revealed that increasing the dose from level 1 and, therefore, including a background infusion did not result in lower pain scores.

These findings appear to contradict those of a recent study that concluded that systemically administered opioids had no significant analgesic effect in labour. In this small study, pain scores during established labour were compared at baseline, and after three contractions, after an i.v. dose of morphine or pethidine. It is not possible to continue the comparison of the two studies further as in our study the subsequent doses of remifentanil were not constant. It would seem likely that remifentanil has a better analgesic effect than pethidine or morphine, although it is difficult to be certain of equivalence in dosage. Further studies are needed.

The maternal safety of the level 1 dose range was also well demonstrated in our study as all adverse events occurred at level 2 or 3. In our study, 5/21 (24%) women had at least one episode of significant desaturation whilst using the remifentanil PCA. This compares favourably with an incidence of desaturation of 42% in women using entonox during labour. We recommend, however, that pulse oximetry monitoring is carried out on all women using a remifentanil PCA in labour until more information is available. Adding a background infusion does not reduce pain scores but serves only to increase respiratory depression and sedation.

The incidence of vomiting was high, occurring in 10/21 (48%) women. However, only three women required anti-
emetics and only 3/21 women vomited whilst using remifentanil at the level 1 dose range. The occurrence of vomiting in low-risk normal labour has been reported to be as low as 19%\textsuperscript{24} However, when pethidine is used for analgesia in labour, vomiting has been reported in 40% of women,\textsuperscript{2} which approximates to our incidence of 48%. Itch was reported in 12/21 (57%) women but this was described as mild and required no specific treatment.

Fetal heart rates, Apgar scores, and cord pH values were satisfactory. It was particularly reassuring that, despite remifentanil being available to the women at delivery, all Apgar scores at 5 min were in the normal range of 8–10 and that no baby required naloxone to establish spontaneous respiration. A forthcoming study will investigate cardiotocograph changes and the neurological and adaptive capacity score associated with using the remifentanil PCA.

In conclusion, remifentanil PCA with a bolus dose in the range 0.25–0.5 μg kg\textsuperscript{−1} and a lockout time of 2 min appears a safe and effective drug for use in labour in patient-controlled analgesia systems. The technique appears to be most beneficial in multiparous women, 73% of whom chose to use the remifentanil PCA alone for their entire labour and delivery.

References

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