Remifentanil patient-controlled analgesia effect-site target-controlled infusion compared with morphine patient-controlled analgesia for treatment of acute pain after uterine artery embolization

M. Lipszyc1, E. Winters2, E. Engelman3*, M. Baurain3 and L. Barvais3

1 Department of Anaesthesia, Institut Jules Bordet, Boulevard de Waterloo 121, 1000 Brussels, Belgium
2 Department of Anaesthesia, Onze Lieve Vrouweziekenhuis, Moorselbaan 164, 9300 Aalst, Belgium
3 Department of Anaesthesia, Erasme Hospital, Route de Lennik 808, 1070 Brussels, Belgium

* Corresponding author. E-mail: eengelma@ulb.ac.be, edgard.engelman@skynet.be

Background. Post-procedural pain control after uterine artery embolization (UAE) of urethral leiomyomata remains a major problem.

Methods. This double-blind, randomized study tested the possibility to obtain a quicker onset of analgesia by using effect-compartment controlled remifentanil patient-controlled analgesia (remifentanil TCI-PCA) than by using i.v. morphine PCA. Both systems were connected to an i.v. catheter. Active drug or matching placebo administration was activated by a single push-button. Pain was assessed using a numerical rating scale (NRS) from 0 to 10.

Results. NRS values were lower in the remifentanil group (with a possible difference from two to seven points on the scale) during the initial 4 h of drug administration. After the fourth hour, the NRS values were identical between the groups. No major respiratory or haemodynamic side-effect was observed.

Conclusions. Remifentanil PCA-TCI with a slow and progressive adapted algorithm without any associated premedication or co-medication is feasible in young healthy women undergoing UAE.

Keywords: analgesia, patient-controlled; anaesthetics, i.v./administration and dosage; leiomyoma/therapy; substances, remifentanil–morphine

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Leiomyomata are the most common female reproductive tract tumours. They affect one in four Caucasian women between the age of 40 and 60 yr old.1 Uterine artery embolization (UAE) is a minimally invasive treatment alternative to hysterectomy and myomectomy that has rapidly gained in popularity and acceptance. UAE was first described by Ravina and colleagues2 in 1995 as a treatment of uterine myomata. Since then, large series have been published describing the benefits, risks, and the advantages over surgery.3 The fact that UAE preserves the uterus motivates many patients to choose for this technique.4–6

Post-procedural pain control after UAE remains a major problem.7 Pelvic cramping most likely due to post-embolization myometrial ischaemia and fibroid infarction causes this pain.8 Even if successful outpatient UAE has been described, it requires an effective pain treatment such as epidural analgesia or high doses of i.v. opioids,7 mostly morphine which requires sometimes overnight hospitalization.9 In the study by Kim and colleagues,10 99% of the women required i.v. opioid patient-controlled analgesia (PCA).

PCA is considered a very effective method to administer opioids during the post-anaesthesia period.11 PCA remifentanil has shown efficacy at the price of a somewhat narrow safety margin.12–13 Schraag and colleagues14 have described the use of remifentanil target-controlled infusion (TCI) by PCA administration in the postoperative period.

A population pharmacokinetic set has been published for remifentanil15 and has been incorporated in effect-site TCI systems which are available in Europe. These remifentanil TCI pumps allow getting a rapid onset and offset of analgesia, mirroring the time course of abdominal cramping observed after UAE procedures.

The primary objective of this study was to compare the efficacy of analgesia and the side-effects observed after
either remifentanil effect-site TCI or the reference method of morphine PCA currently used in our institution to treat the post-UAE pain.

Methods

This study is referenced under number 2010-000000-12 in the European Clinical Trials Database and was accepted by the local human investigation committee. Nineteen female patients, of ASA physical status I or II, undergoing UAE for the treatment of uterine leiomyomata gave written informed consent to participate in this double-blinded, randomized study which was approved by the local human investigation committee. The patients were randomized by blocks of four patients to receive one of the active drugs and the matching placebo using a table of random numbers. This study was undertaken in accordance with the CONSORT guidelines.

A single push-button activated by the patient was connected through a Y-connection to the Abbot™ Pain Management Provider (Abbott Laboratories, North Chicago, IL, USA) and the serial connector of the personal computer, allowing the patient to activate both systems at the same time.

Morphine was administered by a PCA pump (Abbot™ Pain Management Provider, Abbott Laboratories). A 2 mg bolus of morphine was delivered at request with a lock-out of 10 min between dosages and a maximal dose of 30 mg per 4 h of treatment.

Remifentanil was administered with TOOLBOX, a software application designed and developed in the department of Computer Sciences of our faculty. It has been implemented with the same algorithms as those proposed by Shafer and Gregg. Remifentanil was infused using the pharmacokinetic and pharmacodynamic model described by Minto and colleagues. The personal computer (PC) was connected to an electric syringe pump (Pilote C, Becton Dickinson Infusion System, Brezins, France). After each demand, the TOOLBOX system increased the remifentanil target effect-site concentration (Ce) by 0.5 ng ml⁻¹ as long as the Ce was < 2.5 ng ml⁻¹; above this Ce, each demand increased the Ce by 0.2 ng ml⁻¹. The patient could increase the Ce of remifentanil as soon as the Ce from the previous demand was reached, without further lock-out time. In the absence of a demand during a 30 min period, the system automatically decreased the target Ce by 0.2 ng ml⁻¹.

Both systems were connected to the same i.v. catheter.

Before the beginning of the radiological procedure until the end of the study, the patients were connected to the administration systems and the monitoring equipment described hereafter. Oxygen supplementation was provided through nasal prongs.

Although this procedure was conducted under local anaesthesia, patients were free to use the PCA pumps from the very beginning.

The active drug solutions consisted of 90 ml normal saline containing 2 mg ml⁻¹ morphine for the Abbot™ Pain Management Provider, or 50 ml syringes with normal saline containing remifentanil 2 μg ml⁻¹ for the TOOLBOX system. These solutions and their identically looking matching placebos containing only normal saline (all were clear solutions) were prepared at the hospital’s pharmacy, with a pharmacist responsible for the randomization. Consecutive patients received the consecutively numbered packages.

For safety evaluation, the patients were monitored by a capnograph using nasal prongs (Microcap, Oridion Medical Ltd, Jerusalem, Israel). Transcutaneous oxygen saturation (SpO₂, Tc) and heart rate were measured continuously (SATLITE TRANS™ OPL-200, Datex Instruments, Helsinki, Finland). These two devices were connected to the PC and a digital value of the SpO₂, the ventilatory frequency, the SpO₂, Tc, and the heart rate were recorded every 5 s.

Non-invasive arterial pressure was measured by an automatic blood pressure monitor (PRESS-MATE BP-8800 Series, Colin Corporation, Komaki-City, Aichi, Japan) at the same time the numerical rating scale (NRS) for pain was evaluated.

A file containing the target effect-site concentration, the infusion rate, the plasma concentration, the effect-site concentration, the SpO₂, the ventilatory frequency, the SpO₂, Tc, and the heart rate was generated by the PC. This file also contained the markers for demand to increase the remifentanil concentrations and the automatic decreases by the TOOLBOX system. The cumulated numbers of demands at each NRS measurement were read from the Abbot™ Pain Management Provider.

In the post-anaesthesia care unit (PACU), side-effects and rescue treatments were also recorded. A patient requesting additional analgesia could receive i.v. paracetamol 1 g every 6 h and i.v. diclofenac 75 mg every 12 h.

Statistical analysis

Evaluation of efficacy

The primary endpoint was the measurement of pain intensity evaluated using an 11-point NRS (0 = no pain and 10 = worst pain possible). These evaluations were made at the end of the procedure, and at the PACU, at 15 min intervals during the first 2 h of stay, and thereafter 4, 8, 12, and 16 h after arrival at the PACU.

The cumulated number of PCA demands made by the patients at each time of NRS evaluation served as additional surrogate endpoints for efficacy.

These parameters of efficacy were compared between the two groups using a multivariate analysis of variance for repeated measures followed by pre-planned comparison at each time of measurement. For each time of measurement, the 95% confidence interval for the difference in the means was computed to allow the clinical significance of the difference between the groups to be assessed. Within each group, each measurement was compared with the measurement made at the previous time.

Post hoc analysis in the remifentanil group

Prediction probabilities for satisfactory analgesia were calculated by applying probit analysis; this allowed the production of a graph correlating the probability of satisfactory
analgesia with Ce remifentanil. In the model, the presence of satisfactory analgesia is defined by the automatic initiation of a decrease in Ce of remifentanil because of the absence of a PCA demand during the past 30 min. The absence of satisfactory analgesia is defined as the presence of a PCA request by the patient.

Evaluation of safety

Respiratory safety

The values of the continuously recorded $\frac{E}{\text{CO}_2}$ values were divided into three categories: 30–40, 40–50, and >50 mm Hg. The values of the continuously recorded $S_p\text{O}_2$ values were divided into three categories: <90%, 90–95%, and 96–100%. The values for ventilatory frequency were divided into four categories: <8, 8–12, 13–25, and 25–40 bpm.

The results for each parameter were expressed as the percentage of the total number of data for each of the two groups, for the parameter in question. The distributions in categories were compared between the two groups using the $\chi^2$ test.

Because these analyses compared several thousand data for each parameter, even small differences will be statistically significant; therefore, the confidence interval, including the real difference between the two groups, was computed at the 95% confidence level to allow the clinical significance of the difference to be assessed.

Using probit analysis, we constructed in the remifentanil group a graph correlating the Ce remifentanil to the probability of measuring an $\frac{E}{\text{CO}_2}$ concentration ≥45 mm Hg by the nasal prongs.

Haemodynamic safety

The values of the continuously recorded heart rate were divided (categorized) in four categories: 35–50, 51–75, 76–100, and 101–125 beats min$^{-1}$. The results for each category are expressed as the percentage of the total number of data for each of the two groups, for the parameter in question. The distributions in categories were compared between the two groups using the $\chi^2$ test, and the 95% confidence interval for the differences between groups was computed.

The values of systolic arterial pressure were compared between the two groups using a multivariate analysis of variance for repeated measures assessing the difference between the groups (between-group effect). For each time of measurement, the 95% confidence interval for the difference in the means was computed to allow the clinical significance of the difference between the groups to be assessed.

Systat v 5.0 for DOS (Systat Software, Inc., Chicago, IL, USA), was used to generate the frequency tables and execute all the statistical analysis with the exception of the computation of the confidence intervals which were calculated with the software package Lotus 1-2-3 97 Edition (IBM, Armonk, NY, USA) using the equations from Gardner and Altman.$^{18}$ For all statistical tests, a $P$-value of <0.05 was considered as statistically significant.

Results

Nineteen patients were included in the study, 10 in the remifentanil group and nine in the morphine group. The study was discontinued in one patient of the morphine group because of a technical failure of the computer system. All the results are given with this patient excluded; this per-protocol analysis is justified by the very experimental status of the remifentanil PCA device, and the results are thus valid for a normally functional system.

The UAE procedure lasted 103.2 (78) and 55.5 (16) min, respectively, in the remifentanil and morphine groups ($P$=0.1).

Analgesic efficacy

The NRS values were statistically lower in the remifentanil group (Fig. 1) for the measurements made from 15 min after arrival in the PACU up to 2 h after arrival. Thereafter, the NRS values in the morphine group decreased which resulted in similar values between the groups. During the first 2 h period, it appears from the computation of the confidence intervals for the difference that a minimum difference of two to four points on the NRS scale can be expected in favour of the remifentanil group with a 95% probability and that differences up to seven points are not excluded.

Figure 2 represents the effect-site concentrations in the remifentanil group at the time of NRS measurement. The mean values are between 2 and 3 ng ml$^{-1}$, with confidence intervals showing that the patients maintained Ce values between 1.5 and 3.5 ng ml$^{-1}$.

Figure 3 shows the cumulated probability of satisfactory analgesia provided by remifentanil. The Ce for remifentanil predicting a 95% (ED$_{80}$) probability for accurate analgesia was 2.98 ng ml$^{-1}$. The ED$_{80}$ was 2.16 ng ml$^{-1}$.

In the morphine group, the cumulated amount of morphine received after 4 h was 21.25 (3.01) mg (Table 1) out of a theoretical maximum of 30 mg. During the next 4 h periods, the amounts of morphine requested by the patient decreased and were significantly lower compared with the initial 4 h period (Table 1).

The cumulated number of PCA demands made by the patients (Fig. 4) was significantly lower in the remifentanil group during the first 4 h after arrival at the PACU. During that period, the mean number of PCA demands in the morphine group was more than double than in the remifentanil group.

Rescue therapy

One patient in each group required rescue pain therapy: in the remifentanil group, one patient received two combined i.v. administrations of paracetamol and diclofenac, whereas the patient of the morphine group received paracetamol i.v. and the 4 h limit of the PCA was raised from 30 to 40 mg.

During the following day, two patients in the remifentanil group received opiates but none in the morphine group. Paracetamol, diclofenac, or both was administered, respectively,
in 80% of the patients in the remifentanil group and 77% in the morphine group.

**Safety and side-effects**

For the ventilatory frequency, there were a higher percentage of values lower than 13 bpm in the remifentanil group (Table 2). However, this difference did not result in a greater proportion of high values of $E_{CO_2}$ values (>$50 \text{ mm Hg}$). Moreover, there were a greater proportion of values in the 30–40 mm Hg category in the remifentanil group (Table 2).

In the remifentanil group, 81.7% of the $E_{CO_2}$ values higher than 40 mm Hg were recorded during the first 4 h

![Fig 1](image1.png) **Fig 1** NRS values for pain (0=no pain and 10=worst pain possible). Data displayed are given as mean with sd.

![Fig 2](image2.png) **Fig 2** Simulated target effect-site concentration of remifentanil in the remifentanil group, from the time of arrival in the PACU to 16 h after arrival. Data displayed are given as mean with 95% confidence interval.
postoperatively, but only 56.6% of these higher values were recorded during that period in the morphine group. After that period, $E_{\text{CO}_2}$ values higher than 40 mm Hg are observed more frequently in the morphine group. Figure 5 correlates the probability of an $E_{\text{CO}_2}$ $\geq$ 45 mm Hg and a Ce of remifentanil. At the Ce remifentanil ED$_{95}$ value (2.98 ng ml$^{-1}$), there was a probability of 6.7% to measure an $E_{\text{CO}_2}$ $\geq$ 45 mm Hg; at the ED$_{80}$ value (2.16 ng ml$^{-1}$), this probability decreased to 3.8%.

The values for transcutaneous oxygen saturation were essentially identical between the groups (Table 2). Heart rates between 35 and 50 beats min$^{-1}$ were more frequent in the remifentanil group than in the morphine group. None of these episodes of bradycardia required a treatment. The systolic arterial pressure values were identical between the groups.

Nausea, vomiting, or both was observed in two patients of the remifentanil group and one of the morphine group. No pruritus was reported.

**Discussion**

Low-dose remifentanil infusion with intermittent bolus injections has been demonstrated to provide adequate sedation, amnesia, and comfort during colonoscopy. On the contrary, continuous remifentanil infusion (0.05–0.15 $\mu$g kg$^{-1}$ min$^{-1}$) used to provide postoperative analgesia after major surgery was associated with an incidence of more than 10% of respiratory adverse events. PCA with remifentanil has been effective during labour or lithotripsy, and when used as a combination of fixed continuous infusion with fixed bolus on patient’s demand, it was associated with similar postoperative analgesia and cardiovascular side-effects to those achieved by morphine PCA after abdominal surgery. In 200 consecutive women undergoing UAE, morphine PCA was more effective in reducing post-UAE pain than fentanyl PCA. The addition of ketamine to i.v. morphine PCA failed to demonstrate a reduction in the amount of morphine required for pain control during the first 24 h after UAE. Up to now, no study has evaluated the interest of remifentanil analgesia in the context of UAE, and there exists no comparative study of effect-site remifentanil TCI-PCA administration after any type of intervention.

### Analgesic efficacy

Considering the profile of the NRS values measured in our two groups, pain rose quickly and reached its maximum intensity during the first hour and remained stable during the following hour after which it decreased slowly. However, the need for i.v. opioids remained 16 h after the procedure as shown by the still existing patient’s demands observed during this period in both groups, and the need for non-opioid analgesics during the following days.

In the context of this study, no residual intraoperative analgesia level was present at the start of the study drug administration. The remifentanil effect-site TCI-PCA algorithm achieved effective pain relief (NRS$<$4) within 15 min after arrival in PACU without clinically important respiratory adverse events. On the contrary, the conventional morphine PCA algorithm used needed 240 min to provide this level of pain relief. Thereafter, both treatments showed similar efficacy. It can be argued that much better results could be obtained by using morphine if the PCA was preceded by a larger loading dose of morphine titrated to the patient’s needs but this could offset the safety of the system or imply the presence of trained anaesthetic or nursing staff.

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**Table 1** Cumulated amount of morphine in the morphine group. Data are presented as mean (so). Multivariate analysis of variance for repeated measures by 4 h periods: $F$=9.07, $P$=0.0007. *$P$<0.05 vs previous measure

<table>
<thead>
<tr>
<th>Time in PACU</th>
<th>Morphine (mg) By 4 h periods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival</td>
<td>3.5 (2.6)</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>5.7 (2.2)</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>8.2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>45 min</td>
<td>10.2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>12.2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>1 h 15 min</td>
<td>14.0 (1.5)</td>
<td></td>
</tr>
<tr>
<td>1 h 30 min</td>
<td>15.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>1 h 45 min</td>
<td>17.5 (1.4)</td>
<td></td>
</tr>
<tr>
<td>2 h</td>
<td>18.7 (1.5)</td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>21.2 (3.0)</td>
<td>21.2 (3.0)</td>
</tr>
<tr>
<td>8 h</td>
<td>31.0 (12.4)</td>
<td>9.7 (10.4)*</td>
</tr>
<tr>
<td>12 h</td>
<td>38.3 (13.6)</td>
<td>8.0 (4.9)</td>
</tr>
<tr>
<td>16 h</td>
<td>42.4 (14.9)</td>
<td>4.1 (3.6)</td>
</tr>
</tbody>
</table>
The greater number of demands to the PCA pump observed in the morphine group is most probably related to the difference in pharmacokinetic profiles of the two opioids and the set-up of their delivery system.

Safety of remifentanil effect-site TCI vs standard morphine PCA

Patients in the remifentanil group experienced more episodes of slow ventilatory frequencies than in the morphine group. This difference can be explained by the difference between the two treatment groups to reach opioid

**Table 2** Safety parameters. Continuous recording of ventilatory frequency, end-tidal CO₂ (E′_CO₂), transcutaneous oxygen saturation (S_pO₂ Tc), and heart rate. Percentage of data recorded in each category of values. Intergroup difference for the difference in categories (χ² test): P<0.000001

<table>
<thead>
<tr>
<th>Ventilatory frequency (bpm)</th>
<th>Remifentanil group</th>
<th>Morphine group</th>
<th>Confidence interval for the difference (95% level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>3.76</td>
<td>0.91</td>
<td>2.18–3.51</td>
</tr>
<tr>
<td>8–12</td>
<td>18.03</td>
<td>13.61</td>
<td>3.79–5.04</td>
</tr>
<tr>
<td>13–25</td>
<td>72.92</td>
<td>77.71</td>
<td>−5.12 to −4.45</td>
</tr>
<tr>
<td>25</td>
<td>5.29</td>
<td>7.77</td>
<td>−3.12 to −1.82</td>
</tr>
<tr>
<td>40</td>
<td>40.6</td>
<td>33.8</td>
<td>6.4–7.2</td>
</tr>
<tr>
<td>E′_CO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>40.6</td>
<td>33.8</td>
<td>6.4–7.2</td>
</tr>
<tr>
<td>40–50</td>
<td>58.1</td>
<td>64.9</td>
<td>−7.2 to −6.4</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1.3</td>
<td>1.3</td>
<td>−0.09 to +0.09</td>
</tr>
<tr>
<td>S_pO₂ Tc (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>0.76</td>
<td>0.96</td>
<td>−0.91 to +0.51</td>
</tr>
<tr>
<td>90–95</td>
<td>4.19</td>
<td>4.97</td>
<td>−1.48 to −0.08</td>
</tr>
<tr>
<td>96–100</td>
<td>95.06</td>
<td>94.07</td>
<td>−0.82 to +1.16</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–50</td>
<td>2.12</td>
<td>0.11</td>
<td>1.28–2.73</td>
</tr>
<tr>
<td>51–75</td>
<td>67.14</td>
<td>61.91</td>
<td>4.80–5.65</td>
</tr>
<tr>
<td>76–100</td>
<td>23.08</td>
<td>37.59</td>
<td>−15.11 to −13.90</td>
</tr>
<tr>
<td>101–125</td>
<td>7.66</td>
<td>0.40</td>
<td>6.55–7.96</td>
</tr>
</tbody>
</table>

![Fig 5](image-url) Prediction probabilities of measuring by the nasal prongs an E′_CO₂ concentration ≥45 mm Hg calculated by applying probit analysis.

The greater number of demands to the PCA pump observed in the morphine group is most probably related to the difference in pharmacokinetic profiles of the two opioids and the set-up of their delivery system.
concentrations able to provide a rapid adequate analgesia. However, during the first 4 h period, episodes of high expired CO2 values or hypoxemia were rare and with a similar incidence. Although the distribution of recorded SpO2 in the two groups is statistically different, it is not clinically relevant. Between 4% and 5% of the recorded oxygen saturation data are between 90% and 95% of oxygen saturation, whereas <1% of the measurements is lower than 90% in both groups.

This absence of acute adverse respiratory events using remifentanil by PCA for pain management in spontaneously breathing patients had already been described in different clinical situations. In 10 spontaneously breathing patients after cardiac surgery, the ventilatory frequency was always >9 bpm with a lowest oxygen saturation recorded at 95% with oxygen supplemented at 2 litre min⁻¹. In 100 patients undergoing extracorporeal shock wave lithotripsy under remifentanil infusion of 0.05 μg kg⁻¹ min⁻¹ combined with patients on a demand bolus of 10 μg of remifentanil, no episode of respiratory depression was observed during the procedure.²¹

Of course, the major limitation of this study is the limited number of patients. For this reason, we can only conclude that the concept of effect-site remifentanil TCI-PCA system with an appropriate algorithm of slow increment and decrement steps has to be tested over a large population and in other clinical situations. An eventual upper and lower limit of the effect-site remifentanil concentration using the Minto pharmacokinetic model should probably be added in the algorithm as an extra safety measure. Our results as presented in Figures 3 and 5 could be helpful in this.

In conclusion, remifentanil PCA effect-site TCI with a slow and progressive adapted algorithm without any associated premedication or co-medication is feasible in young healthy women undergoing UAE. It provides a quicker onset pain relief than the standard morphine PCA with no major respiratory or haemodynamic side-effects.

Conflict of interest
None declared.

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