Remifentanil in labour analgesia – where are we in 2017 – an update.

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Disclosures

• None...
Agenda

• Pharmacology
• Does it work?
• Whys use it at all?
• Conclusion
Remifentanil - Pharma

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Pharmacology

- Highly lipid soluble μ-receptor agonist opioid
- 70% proteinbound
- Esthersray linkage - undergoes rapid hydrolysis to remifentanil acid by tissue and plasma estherase, T1/2: 1-5min
- Context sensitive half-life 3-4 minutes
- Potency = 2x fentanyl, 100-200x morphine
- Lower plasma concentration in pregnancies versus non-pregnancies – large variability

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Fetal exposure

• Uterine vein/Maternal artery ratio: 0.88
• Umbilical artery/umbilical vein ratio: 0.29
  – Redistribution, rapid fetal metabolism
Is it in use??
Remifentanil patient-controlled analgesia

Mid Essex Hospital Services NHS Trust

Norfolk and Norwich University Hospitals NHS Trust

Patient Controlled Analgesia (PCA) in Labour using Remifentanil

SCOPE (Area): Maternity Unit
SCOPE (Staff): Medical, Nursing, Midwifery

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Regimen
Concentration of Remifentanil: 20mcg/ml (2mg Remifentanil in 100ml NaCl 0,9%)
Bolus: 10-30 μg
Lockout interval: 2 min
No additional infusion of remifentanil. No application of any other opioid or analgesic drug.

https://www.google.com/maps/d/viewer?mid=1BrSGgixaIx0JjdvPPBPbHjzlkUA&usp=sharing

2017: 7800 deliveries

26.6% Hypoxia
26% Sedation
17% Nausea
Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. **ULTIVA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate.** Opioid analgesics, including ULTIVA, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.


The ideal opioid delivery

Does not exist!

Pain intensity and effect
Opioids and labour analgesia...
Lack of analgesic effect of systemically administered morphine or pethidine on labour pain

*Ch. Olofsson Senior Registrar, *A. Ekblom Senior Registrar,
**G. Ekman-Ordeberg Consultant, **A. Hjelm Senior Registrar, *L. Irestedt Consultant

Departments of *Anaesthesiology and Intensive Care and **Gynaecology and Obstetrics, Karolinska Hospital, Stockholm, Sweden

Fig. 1. Pain intensity before and following morphine (dose 0.05 mg/kg body weight) or pethidine (dose 0.5 mg/kg body weight) given intravenously at iterative doses. Values are presented in box plot with median and interquartile range and total range indicated by vertical whiskers. No significant effect was found after each dose.

■ = morphine; □ = pethidine.
Parenteral opioids for labor pain relief: A systematic review

Leanne Bricker, MRCOG, and Tina Lavender, PhD

Liverpool, England

Parenteral opioids are commonly used for labor pain relief and have been so for many years. The objectives of this review were to determine the safety and efficacy of opioids in this context. Of 85 trials systematically reviewed, 48 comprising more than 15,000 women, the number of trials contributing data to individual outcome measures was sufficient to compare better pain relief. However, if women opt for systemic analgesia, no strong conclusions can be recommended. Pethidine is the most commonly used opioid worldwide, but considerable doubts about its analgesic effectiveness and concerns about its potential maternal, fetal, and neonatal side effects, it has the virtue of familiarity and low cost. There is as yet no convincing research evidence to show that alternative opioids are better. In view of the large number of women who receive opioids in labor and the paucity of research evidence about the relative effectiveness and side effects of different opioids and opioids compared with other methods (apart from epidural), well-designed and suitably sized trials of pethidine versus the main alternatives that address substantive outcomes for mothers and babies are strongly recommended. (J Am Obstet Gynecol 2002;186:S94-109.)
A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia

Patricia K. Morley-Forster MD,
Donald W. Reid MD,
Hilde Vandeberghe PhD

Purpose: To determine the analgesic efficacy of equipotent doses of PCA (patient-controlled analgesia) fentanyl and PCA alfentanil for labour pain.

Methods: Twenty-three, ASA I - ll parturients between 32-42 wk gestational age in whom epidural analgesia was contraindicated were randomized to receive PCA fentanyl (Group F) or alfentanil (Group A). Plain numbered vials contained 21 ml fentanyl 50 \( \mu \)g·ml\(^{-1} \) or alfentanil 500 \( \mu \)g·ml\(^{-1} \). A one millilitre loading dose was administered. The PCA solution was prepared by diluting 10 ml study drug with 40 ml saline and the PCA pump was programmed to deliver a dose of 2 ml, delay of five minutes and a basal rate of 2 ml·hr\(^{-1} \). Maternal measurements obtained were hourly drug dose, total dose, Visual Analog Pain Score (VAPS) q 30 min, sedation score q 1 hr and side effects. Neonates were assessed by 1.5, and 10-min Apgar scores, umbilical venous and arterial blood gases and neurobehavioural scores at four and 24 hr.

Results: Mean VAPS from 7 - 10 cm cervical dilatation were higher in Group A than in Group F. (85.7 ± 13.9 vs 64.6 ± 12.1; \( P < 0.01 \)). There were no inter-group differences in VAPS from 1 - 3 cm, or from 4 - 6 cm dilatation, in maternal sedation scores or side effects, or in neonatal outcomes.

Conclusion: In the doses prescribed in this study, PCA fentanyl was found to provide more effective analgesia in late first stage labour than PCA alfentanil.
### Table 2  Studies of remifentanil patient-controlled intravenous analgesia in labor

<table>
<thead>
<tr>
<th>Study</th>
<th>Bolus (µg/kg)</th>
<th>Lockout (min)</th>
<th>Infusion rate (µg/kg/min)</th>
<th>Maximum hourly dose (µg)</th>
<th>Number of remifentanil patients</th>
<th>Alternative analgesia required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olufolabi 2000</td>
<td>0.25–0.5</td>
<td>2–5</td>
<td>0</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Blair 2001</td>
<td>0.25–1.0</td>
<td>2</td>
<td>0.0–0.05</td>
<td>NR</td>
<td>21</td>
<td>38% (epidural)</td>
</tr>
<tr>
<td>Volikas 2001</td>
<td>0.5</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>9</td>
<td>45% (nitrous oxide); 11% (epidural)</td>
</tr>
<tr>
<td>Volmanen 2002</td>
<td>0.2–0.8</td>
<td>1</td>
<td>0</td>
<td>No limit</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Thurlow 2002</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>NR</td>
<td>18</td>
<td>55% (nitrous oxide)</td>
</tr>
<tr>
<td>Blair 2005</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>20</td>
<td>90% (nitrous oxide)</td>
</tr>
<tr>
<td>Volmanen 2005</td>
<td>0.4</td>
<td>1</td>
<td>0</td>
<td>No limit</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Evron 2005</td>
<td>20–70</td>
<td>3</td>
<td>0</td>
<td>No limit</td>
<td>43</td>
<td>NR</td>
</tr>
<tr>
<td>Volikas 2005</td>
<td>0.50</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>Balki 2007</td>
<td>0.25–1</td>
<td>2</td>
<td>0.075–0.1</td>
<td>NR</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Volmanen 2008</td>
<td>0.1</td>
<td>1</td>
<td>0</td>
<td>NR</td>
<td>27</td>
<td>NR</td>
</tr>
<tr>
<td>D’Onofrio 2009</td>
<td>0</td>
<td>0</td>
<td>0.025–0.15</td>
<td>NR</td>
<td>205</td>
<td>11% (epidural)</td>
</tr>
<tr>
<td>Douma 2010</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>52</td>
<td>14% (epidural)</td>
</tr>
<tr>
<td>Douma 2011</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>5% (epidural)</td>
</tr>
<tr>
<td>Volmanen 2011</td>
<td>0.4</td>
<td>1</td>
<td>0</td>
<td>NR</td>
<td>45</td>
<td>NR</td>
</tr>
<tr>
<td>Ng 2011</td>
<td>25–30</td>
<td>3.75–4.5</td>
<td>0</td>
<td>NR</td>
<td>34</td>
<td>NR</td>
</tr>
<tr>
<td>Marwah 2012</td>
<td>0.25</td>
<td>2</td>
<td>0.025–0.05</td>
<td>3000 over 4 h</td>
<td>47</td>
<td>&gt;40% (pethidine &amp; nitrous oxide)</td>
</tr>
<tr>
<td>Ismail 2012</td>
<td>0.1–0.9</td>
<td>1</td>
<td>0</td>
<td>NR</td>
<td>380</td>
<td>6% (epidural)</td>
</tr>
<tr>
<td>Tveit 2012</td>
<td>0.15</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>19</td>
<td>NR</td>
</tr>
<tr>
<td>Stourac 2012</td>
<td>20 (10 µg increases)</td>
<td>3</td>
<td>0</td>
<td>NR</td>
<td>12</td>
<td>10% (epidural)</td>
</tr>
<tr>
<td>Shen 2013</td>
<td>0.1–0.4</td>
<td>2</td>
<td>0.05–0.2</td>
<td>NR</td>
<td>53</td>
<td>NR</td>
</tr>
<tr>
<td>Stocki 2013</td>
<td>20–60</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>19</td>
<td>11% (epidural)</td>
</tr>
<tr>
<td>Tveit 2013</td>
<td>0.15–1.0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>41</td>
<td>NR</td>
</tr>
<tr>
<td>Lin 2014</td>
<td>0.4</td>
<td>5</td>
<td>0.04–0.05</td>
<td>NR</td>
<td>170</td>
<td>NR</td>
</tr>
<tr>
<td>Freeman 2015</td>
<td>30–40</td>
<td>3</td>
<td>0</td>
<td>NR</td>
<td>402</td>
<td>13% (epidural)</td>
</tr>
</tbody>
</table>

*aComparison of bolus only with continuous infusion. NR: not reported.*

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**Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour**

**Fig 1** Mean VAS pain scores as a function of time for meperidine, remifentanil, and fentanyl. Vertical bars represent standard error of the mean.

were higher with remifentanil, but remifentanil produced more severe periods of desaturation ($S_{a}O_{2} < 95\%$) were observed during administration of remifentanil and fentanyl. There were no significant differences in fetal outcome between the three groups.

**Conclusions.** The efficacy of meperidine, fentanyl, and remifentanil PCA for labour analgesia varied from mild to moderate. Remifentanil PCA provided better analgesia than meperidine and fentanyl PCA, but only during the first hour of treatment. In all groups, pain scores returned to pre-treatment values within 3 h after the initiation of treatment.

Remi: 40µg/2mins
Fenta: 20µg + loading
Pet: 5 mg + loading
Other opioids better?

Remifentanil provides better pain relief than other opioids, but only during the first two hours.
Does it work?
Remifentanil for labor analgesia: an evidence-based narrative review

M. Van de Velde, a B. Carvalho

Volmanen et al. 2008
Douma et al 2011
Tveit et al. 2012
Lin et al. 2014
Volmanen et al. 2005
Marwah et al. 2012
Ng et al. 2011
Douma et al. 2010
D’Onofrio et al. 2009
Balki et al. 2007
Balki et al. 2007
Volmanen et al. 2005
Blair et al. 2005
Evron et al. 2005
Volikas et al. 2001
D’Onofrio et al. 2009
Tveit et al. 2013
Volikas et al. 2005 multipara
Volikas et al. 2005 primipara
Volmanen et al. 2002
Blair et al. 2001

From: M Van De Velde, B Carvalho: IJOA 2016; 25: 66-74
In women in labour, patient controlled analgesia with remifentanil is not equivalent to epidural analgesia with respect to scores on satisfaction with pain relief. Satisfaction with pain relief was significantly higher in women who were allocated to and received epidural analgesia. TRIAL REGISTRATION: Netherlands Trial Register NTR2551.

CONCLUSION: In terms of labor duration, average VAS pain scores, and maternal overall satisfaction score with analgesia, CSE analgesia is superior to that provided by epidural analgesia or PCIA with remifentanil for pain relief in early labor in nulliparous women. However, there were no differences in the mode of delivery, side effects or neonatal outcomes between the three techniques.
Oxygen saturation was significantly lower (SpO2 <92%) in women who used remifentanil (relative risk 1.5, 1.4 to 1.7).


Oxygen saturation was significantly lower (SpO2 <92%) in women who used remifentanil (relative risk 1.5, 1.4 to 1.7).
Meta Analyses

• This meta-analysis suggests that remifentanil PCIA is not superior to epidural analgesia in analgesic efficacy during labor. Given the wide CIs of the pooled results for secondary maternal and neonatal outcomes, definite conclusions cannot be drawn for those outcomes. Further studies are still warranted to validate these conclusions. Liu ZQ, Chen XB, Li HB, Qiu MT, Duan T. A comparison of remifentanil parturient-controlled intravenous analgesia with epidural analgesia: a meta-analysis of randomized controlled trials. Anesth Analg. 2014;118(3):598-603.


• Conclusions: Pooled assessment of remifentanil intervention seems an attractive strategy for controlling labor pain in health term parturients, but it is not supported by strong evidence. Current evidence suggests that it may produce effective analgesia by only a modest level. HealthMED. 2012;6(7):2407-18.

Effect size difference: 3 cm
Patient-controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour (Review)


20 RCT’s, 3569 women
Results Weibel et al..

- Based on the current systematic review, there is mostly low-quality evidence to inform practice and future research may significantly alter the current situation. The quality of evidence is mainly limited by poor quality of the studies, inconsistency, and imprecision. More research is needed on maternal and neonatal safety outcomes (maternal apnoe and respiratory depression, Apgar score) and on the optimal mode and regimen of remifentanil administration to provide high efficacy with reasonable adverse effects for mother and their newborns.
Always satisfied?

Of course they are! Who wouldn’t?

The numbers in parentheses indicate percent.

The mother was asked within six hours of delivery “Overall how would you rate this method of pain relief? Good - Adequate - Inadequate”. There was no difference between groups.
Optimal administration of remi?
Optimal administration of remi?

- Protocols varies (bolus dose, lock-out, background infusion, TCI, etc)
- Fixed bolus 20-50 µg without background infusion, lock-out 2-3 minutes
- If background – small dose < 0.05µg/kgxmin
- TCI? 0.5-1.5 ng/ml
- New systems? VPIA? (Vital signs patient controlled intravenous analgesia)
Fig. 1  Algorithm for vital signs-controlled, patient-assisted intravenous analgesia. SpO₂: maternal arterial oxygen saturation.

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Cont infusion or PCA?

• Shen MK, Wu ZF, Zhu AB, et al. Remifentanil for labour analgesia: a double-blinded, randomised controlled trial of maternal and neonatal effects of patient-controlled analgesia versus continuous infusion (0.005-0.2 µg/kg/min) Anaesthesia. 2013;68(3):236-44. The results suggest that remifentanil PCA (0.1-0.4 µg/kg) provides better pain relief and similar placental transfer compared with continuous infusion. (Author)

• Per protocol TCI Norwegian National Hospital (Oslo University Hospital):
  – 0.5 – 2 ng/ml + nurse controlled boluses) – easier for anaesthesia personell?
Remifentanil TCI?

• **Why not?**
  - 1ng/ml start, incremental doses of 0.5 ng/ml, titrated until satisfied mother or side-effects (1-6 ng/ml).
Why use remifentanil ??
In conclusion...
When to use it?

• For parturients with contraindications to regional analgesia
  – Bleeding disorders
  – Infections?
  – Mother does not want regional

• In places with reduced anaesthesia service?
Then remifentanil is the best choice

- Continuous monitoring
- Including capnography or RR counting
- Well educated staff
Remifentanil PCA

• Is cheap
• Easy to administer
• Gives (some) pain relief
BUT..

• Has a poor analgesic effect compared to the golden standard of regional analgesia
• May cause a lot of harm
• And.....
Is too dangerous to be used as routine analgesia in the labour ward..

AND SHOULD BE RESERVED FOR THE SPECIAL OCCATIONS..
Thank you!
Large randomized prospective trials are required before it may be recommended for routine use in labouring women. © 2013 Elsevier Ltd.