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**Title:** Patient controlled remifentanil and epidural analgesia during labour: satisfaction, costs and safety.  
**Issue Date:** 2016-11-30
General introduction
Background

Obstetric care in the Netherlands is characterised by a decentralised system with independent midwives working in the community. They deliver antenatal care and support delivery at home for women at low obstetric risk. Midwives in the Netherlands operate as autonomous health care professionals and one of their focuses is to prevent unnecessary interventions in low risk pregnancies. Birth is viewed by Dutch midwives and doctors as a physiological process and medical pain relief and interventions are seen traditionally as a last resort in difficult labour. It is important to find the balance between a physiologic approach of labour and the use of technology and interventions to get the best possible outcome for mother and child. Over the past decades we have seen increasing medicalisation of pregnancy and birth, also in the Netherlands, and as a result increasing numbers of women asking for medical pain relief. Traditionally labour pain was viewed as a normal physiological phenomenon that serves a purpose (increasing bond between mother and child). Nowadays, more and more women view labour pain as unnecessary, and because of this are more likely to request medical pain relief during labour. 

Analgesia during labour is an important topic for both pregnant women, caregivers and health care providers. The number of women requesting analgesia in the Netherlands has increased by 1-2% each year in the past decade. Around 170.000 women deliver in the Netherlands each year1 and uptake of analgesia in 2010 was 26.6%, 15% epidural analgesia and 11.6% opioids.2 So, the options of labour analgesia and its availability affect at least 40.000 women in the Netherlands yearly. Epidural analgesia is considered the most effective method of pain relief and is recommended as first choice by the Dutch Colleges of Obstetricians and Anaesthesiologists.3 Not all women can receive epidural analgesia due to contra-indications and some women prefer other methods of analgesia.

Pain during labour

The experience of pain during labour is the result of complex processing of multiple physiologic and psychosocial factors on a woman’s individual interpretation of painful stimuli.4 Unlike any other pain experience; labour pain is not associated with pathology but accompanies a physiological process. Historically, labour pain is explained as enabling labouring woman to seek assistance and find a safe place to give birth. Also, the effect of the production of endogenous endorphins and oxytocin is thought to result in a positive effect on the bond between mother and child.5 The percentage of women that rate pain during labour as severe or unbearable varies between studies and has been reported as high as 80-90%.3 Labour pain is rated as more painful than most other painful conditions, only surpassed by causalgia and amputation.6
Methods of pain relief

Pain relief during labour can be divided into medical and non-medical methods. Examples of non-medical methods are psychoprophylaxis, hypnobirthing, and continuous one-to-one support by doula or midwife, immersion in water, sterile water injections and transcutaneous electro neural stimulation (TENS). Methods of medical pain relief available in the Netherlands are intravenous or intramuscular opioids (meperidine, morphine, remifentanil), nitrous oxide and epidural analgesia (either continuous or patient controlled). The focus of this thesis is medical pain relief, in particular remifentanil PCA and epidural analgesia.

Epidural analgesia

Indications for epidural analgesia are request for pain relief, insufficient progress of labour and maternal indication (for example cardiac disease or morbid obesity).

There are situations in which epidural analgesia is contra-indicated, i.e. women with coagulation disorders, a common problem in daily obstetrics in preeclampsia and HELLP syndrome, or patients with musculoskeletal disorders.

With epidural analgesia, an epidural catheter is placed into the epidural space to administer medication. A local anaesthetic, administered through this catheter, is used to block transmission of afferent pain stimuli across sensible nerve tracts, however, depending on the anaesthetic and amount of this anaesthetic used this can also lead to interruption of motor tracts which causes impairment of movement, decreased pelvic tone and interferes with the bearing down effort in the second stage. In the early years a significant loss of motor function was an important problem, this was attributed to the local anaesthetic used. This is undesirable during labour. The newer long-acting anaesthetics like ropivacain have lower toxicity and less effect on motor function. Adding an opiate to continuous infusion has the benefit of less need for high doses of local anaesthetic and reduction of the risk of a motor block which reduces the risk of adversely affecting the course of labour.

Because there are only small and non-significant differences in efficacy and side-effects between local analgesics and opioids that are used for epidural analgesia during labour, there is considerable variation in medication and dosage administered in epidural analgesia. Various regimes of local anaesthetic and opioid are considered safe and efficient. One explanation for this variation could be preference of the anaesthesiologist. Another might be costs, for example the cost of ropivacain is about seven times the cost of bupivacaine.

Epidural analgesia can be administered by continuous infusion through the catheter, combined with spinal analgesia (CSE) or patient controlled analgesia (PCEA); safety profiles are comparable for all three techniques. Pain reduction in the first hour is better with CSE but hypotension is seen more frequent. The advantage of PCEA is an added effect of being in control on satisfaction and less use of local anaesthetic.

Epidural analgesia provides better pain relief than parenteral opioids with a mean difference in VAS pain intensity score of 40 mm (scale 100 mm) during the first stage of labour. Side-effects
that are associated with epidural analgesia are increased use of oxytocin to augment labour, a longer duration of the second stage of labour (mean difference 15 min), increased risk of vaginal instrumental delivery, maternal temperature ≥38°C, hypotension, urinary retention and post spinal headache.\(^7,9\)

Cochrane meta-analysis of epidural analgesia versus other methods of medical pain relief (parenteral opioids/nitrous oxide) showed no difference in low Apgar score (<7) at 5 minutes but a lower risk of umbilical cord pH <7.20 (RR 0.80 95% CI 0.66-0.96) and less need for naloxone (RR 0.13 95% BI 0.08-0.21) in the epidural analgesia group.\(^7\) Leighton et al showed no significant difference in low Apgar score (<7) at 5 minutes, low umbilical cord pH, meconium aspiration or neonatal asphyxia in their meta-analysis.\(^8\)

**Opioids/meperidine**

An alternative to epidural analgesia is systemic analgesia with opioids. This can be used by women in whom neuraxial analgesia is contraindicated, refused or simply not needed. The most frequently used alternative to epidural analgesia in the Netherlands was intramuscular meperidine which has been used as analgesia during labour for almost 80 years. Meperidine exerts analgesic effects by acting as an agonist to \(\mu\)-opioid receptors. Meperidine is an opioid with a half-time of 2-3 hours but its metabolite norpethidine has a half-time of 8-12 hours. It seems to provide better analgesia than placebo with around 25% of women achieving satisfactory analgesia\(^10\) although this is challenged by an RCT performed in 1996. This trial did not find improvement in pain intensity scores in women with a baseline VAS score of 9 who were treated with meperidine or morphine.\(^11\) Most common maternal side-effects of meperidine are sedation, nausea and vomiting. With birth within 1-3 hours after maternal meperidine, there is an increased risk of neonatal depression (low Apgar score and lower umbilical cord pH).

**Nitrous oxide**

Nitrous oxide in oxygen (50/50 mixture) has some analgesic effects, especially in short term use.\(^12\) The analgesic effects of nitrous oxide are linked to the interaction between the endogenous opioid system and the descending noradrenergic system. Nitrous oxide induced release of endogenous opioids causes disinhibition of brain stem noradrenergic neurons, which release norepinephrine into the spinal cord and inhibit pain signalling. While safe for mother and child there have been concerns with respect to harmful reproductive effects with chronic professional exposure. Because of this nitrous oxide has not been used for over a decade in the Netherlands. Latest research shows that exposure of health care workers with the latest safety precautions stays below the safe limit.\(^13\) So, nitrous oxide is being offered in Dutch hospitals again, especially in birth clinics were women can deliver (and have access to nitrous oxide) while under care of their community midwife.

**Remifentanil patient controlled analgesia**

Remifentanil is a synthetic opioid with direct action on \(\mu\)-opioid receptors. It has a short half-life and latency to peak effect which make it very suitable for administration through patient controlled
analgesia (PCA). Remifentanil is a unique opioid because the elimination half-time (ranging from 10-20 min) is unaffected by hepatic and renal function. Also, most opioids have an increase in context-sensitive half-time (the time necessary to achieve a 50% reduction in drug concentration following a continuous infusion) when administered for longer periods. However, the context-sensitive half-time of remifentanil remains short, 2-5 min, unrelated to duration of infusion. There is no accumulation during repeat bolus infusions. The rapid onset of analgesia (30-60 s), which peaks at 2.5 minutes make remifentanil very suitable for PCA. The timing of each bolus is of vital importance for its analgesic effect. An IV bolus dose at the beginning of a contraction is likely to provide analgesia for the next contraction. Fetal safety of remifentanil has been established by Kan et al. who demonstrated that there is a significant degree of placental transfer of remifentanil (mean umbilical vein-maternal artery ratio 0.88). However, the mean remifentanil umbilical artery: umbilical vein ratio of 0.29 suggests rapid metabolism and rapid redistribution. No differences in Apgar score or fetal acidosis were found.

**Remifentanil in clinical practice**

The first reports on remifentanil as labour analgesia were published in the final years of the last millennium. They described the use of remifentanil as patient controlled analgesia with good analgesic effects in women with contra-indications for regional analgesic techniques with an acceptable safety profile. Remifentanil provides modest analgesia with reduction of pain intensity scores of 15 mm and 30 mm on a 100 mm scale. Conversion rate to epidural analgesia is below 10% in all but one study. Therefore, the majority of women seem satisfied with this modest degree of analgesia. Pain appreciation (satisfaction with pain relief) also seems comparable between remifentanil PCA and epidural analgesia. Two previous studies that assessed satisfaction with pain relief with remifentanil PCA compared to epidural analgesia reported no differences. Both studies, however, had limitations. Volmanen and colleagues limited the observation period to only one hour after the start of pain relief, while Douma and colleagues recorded pain relief scores as a secondary outcome in a study powered to investigate difference in pain scores. In both studies, epidural analgesia was superior to remifentanil PCA in terms improvement of pain intensity scores. The fact that higher pain scores were not reflected in poorer satisfaction scores could be explained by increased pain tolerance or euphoria which is known with opioid use. Another explanation might be that the fact that women can control their analgesia through the PCA device makes them feel more in control of the situation and therefore more satisfied. Last, both studies did not have sufficient power to detect a difference in satisfaction with pain relief.
Dose finding

The efficacy of analgesia might depend on the dose and manner in which it is administered. Remifentanil can be given with just intermittent bolus with a lockout interval or combined with continuous background infusion. There is no consensus on the use of background infusion in remifentanil PCA or on the optimal bolus dosage. One study reported no additional analgesic effect but more maternal side effects with background infusion\(^2\) while another recommended background infusion based on their low conversion rate to epidural analgesia (5%).\(^7\) Most studies used a flexible (weight dependent) bolus dose\(^2\) reporting better pain scores with remifentanil than their comparison. The average bolus dose appears to be 40-50 µg, with a lockout time of 1-2 min.\(^7\) Weighing efficacy against side-effects Hill et al recommend using a bolus dose of 40 µg, with a lockout time of 2 min, in their review.

Side-effects of remifentanil

Maternal safety remains a concern with any opioid based analgesic technique in labour. The main concern with remifentanil PCA is the risk of hypoventilation causing episodes of desaturation. All studies to date have reported maternal oxygen desaturation that has been transient. When compared to meperidine episodes of desaturation are comparable (RR 1.58 95% CI -0.41 to 6.05).\(^1\) When compared to epidural analgesia there is a greater risk of desaturation (RR 16.04 95% CI 3.33 to 77.32).\(^1\) Remifentanil causes maternal sedation compared to epidural analgesia\(^2\) and compared to pethidine and fentanyl PCA.\(^3\)

Another concern that has been raised is that intra-operative use of remifentanil during cardiothoracic surgery is correlated with significant more chronic pain after surgery in a dose dependent manner (odds ratio 8.9, 95% confidence interval 1.6–49.0).\(^3\) A follow up study to the RAVEL trial was designed to assess whether the use of remifentanil during labour could lead to more persistent postpartum pain (PPP).

Economic considerations

Only one study has been published on costs of epidural analgesia versus intravenous opioids.\(^3\) Incremental costs for women treated with epidural analgesia were calculated based on literature review on complications and additional costs of involvement of an anaesthesiologist. They presented that incremental costs based on a societal perspective were $338 ($228 for anaesthesiological involvement and $118 for additional costs made in case of complications). There was no involvement of an anaesthesiologist in administration of intravenous opioids.\(^3\)
This thesis reports on the use of remifentanil PCA and epidural analgesia during labour. Our aim was to report on efficacy (satisfaction with analgesia), cost-effectiveness and safety.

**General background on the RAVEL trial**

The Dutch guideline “Medical pain relief during labour” was published in 2008 and approved by the Colleges of Obstetricians, Anaesthesiologists’ and Midwives (NVOG, NVA, KNOV). It recommends to have epidural analgesia available upon request 24/7 and to use remifentanil PCA only in a controlled, research setting. However, at that time, not all hospitals provided epidural analgesia for all women 24/7 and over 30% of hospitals already used remifentanil outside of clinical trials.³

The RAVEL (Remifentanil patient controlled Analgesia Versus Epidural analgesia in Labour) trial was conducted to answer two primary research questions.

1. **first** the question of equivalence in satisfaction with pain relief of remifentanil PCA and epidural analgesia
2. **second** on the costs of both strategies.

An estimation of the costs of remifentanil PCA versus epidural analgesia before start of the trial showed that there could be a potential reduction of 64 euro per woman. This difference is explained by the extra costs of anaesthesiological and nursing staff. So, provided there would be equality in satisfaction, this could potentially save 1.2-4.6 million euro per year nationwide depending of the number of women asking for pain relief.
Outline of the thesis

In Chapter 1 an introduction on the subject is provided. Chapter 2 presents the results of an online questionnaire on the use of analgesia in the Netherlands. Chapter 3 outlines the study protocol of the RAVEL (Remifentanil patient controlled Analgesia Versus Epidural analgesia in Labour) trial as it was published in BMC Pregnancy and Childbirth.

Chapters 4-5 focus on efficacy and costs while chapters’ 6-8 focus on safety.

In Chapter 4 the results of the efficacy analysis of the RAVEL trial are presented, this multicentre randomised controlled equivalence trial investigating remifentanil PCA and epidural analgesia was conducted in 15 centres in the Netherlands. Primary outcome measure was satisfaction with pain relief. In Chapter 5 the results of the economic analysis of the trial are presented. The economic analysis was done from a health care perspective and calculated costs from the start of labour until 10 days postpartum.

We looked closer at respiratory complications in women receiving analgesia in the RAVEL cohort. The results of this analysis are described in Chapter 6. After the publication of the RAVEL and STER (Saturation and Temperature in Epidural and Remifentanil) studies a meta-analysis on side effects and maternal parameters was performed, the results are presented in Chapter 7. Because of indications that the use of remifentanil is associated with chronic pain we decided on a post hoc follow up study, the results of which are presented in Chapter 8.

The general discussion can be found in Chapter 9.
References


