Patient controlled remifentanil and epidural analgesia during labour : satisfaction, costs and safety

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Satisfaction, costs and safety.

Liv Freeman

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Table of contents

1

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 focusses 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 year[1] 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.[7] 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.[3]

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.[3]

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.[8] 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 at all 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 μ-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 μ-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.[14] 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.[15] The rapid onset of analgesia (30-60 s), which peaks at 2.5 minutes[16] 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.[17] 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[18]. No differences in Apgar score or fetal acidosis were found.[19]

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.[20,21] Remifentanil provides modest analgesia with reduction of pain intensity scores of 15 mm[21] and 30 mm[23] 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.[17] 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.[24,25] 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[26] while another recommended background infusion based on their low conversion rate to epidural analgesia (5%).[27] Most studies used a flexible (weight dependent) bolus dose[22,23,26-30] 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.[17] 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).[19] When compared to epidural analgesia there is a greater risk of desaturation (RR 16.04 95% CI 3.33 to 77.32).[19] Remifentanil causes maternal sedation compared to epidural analgesia[25] and compared to pethidine and fentanyl PCA.[31]

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).[32,33] 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.[34] 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.[34]

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 (**R**emifentanil patient controlled **A**nalgesia **V**ersus **E**pidural analgesia in **L**abour) 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 safe 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**.

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2

Epidural analgesia versus remifentanil patient controlled analgesia in labor: a survey of practice in the Netherlands

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Abstract

Introduction: Epidural analgesia is widely recommended as method of choice for pain relief during labor whereas it is recommended to use remifentanil patient controlled analgesia only in the context of a randomized clinical trial.
The aim of the study was to investigate the availability and use of epidural analgesia and remifentanil patient controlled analgesia, in all Dutch hospitals.

Material and Methods: We extracted data on the use of epidural analgesia as pain relief for women in labor from the Netherlands Perinatal Registry. Because data on remifentanil patient controlled analgesia are not available in the registry, we also sent an anonymous online survey via email to all 90 hospitals with an obstetric ward in the Netherlands. The survey contained questions about obstetric analgesia with a focus on the availability and use of epidural analgesia and remifentanil patient controlled analgesia.

Results: In 2010 15% of 176,810 women giving birth in the Netherlands received epidural analgesia while 11.6 % received opioids. Response rate to the survey was 67% (60). Remifentanil patient controlled analgesia was available in 47% (28). In 67% of those hospitals remifentanil patient controlled analgesia was available for all laboring women whereas 14% only offered it to women with a contra-indication for epidural analgesia. Most hospitals use a flexible background infusion and a bolus dose of 30 μgram. When only epidural analgesia was available 20% of women used pain relief (range 8-43%), versus 38% when epidural analgesia and remifentanil patient controlled analgesia were available (range 26-63%) ($p<0.001$).

Conclusion: Offering epidural analgesia and remifentanil patient controlled analgesia increases the use of analgesia over offering epidural analgesia alone. Despite the recommendation to use RPCA only in an experimental setting, remifentanil patient controlled analgesia is offered in almost 50% of hospitals.

Introduction

Analgesia during labor is an important issue for pregnant women and health care providers. The Dutch multidisciplinary guideline "Pain relief during labor" advises that epidural analgesia (EA) is available for all parturients 24 hours a day as analgesia of first choice.[1] The guideline was written because of existing differences in availability of analgesia between hospitals, increasing demand, and concern about whether a request of women for pain relief during labor could be fulfilled 24 hours a day.[1] There is large variation in the utilization of EA between countries. In the United Kingdom EA is used as analgesia during labor by 28% of women, in contrast to 60% in the USA.[2,3] In the Netherlands, the use of EA during labor is 15%,[4] but increasing. The Dutch obstetrical system is unique in the western world, with a large number of women under the care of community midwives antenatally (primary care). In 2010 83.9% of women started antenatal care in primary care and of those 28.8% delivered in primary care; the remaining women were referred to secondary care either during pregnancy or during labor.[4] Women who deliver under care of their community midwife either deliver at home or in a short-stay hospital setting. Medical pain relief and other medical interventions are not available in primary care. Secondary care consists of three types of hospitals: university, teaching and general. University hospitals are tertiary referral hospitals allied with one of the eight medical schools where specialized antenatal care and neonatal intensive care unit facilities are available. Teaching hospitals are general hospitals that also work with the university medical centers in training of medical interns and residents. They offer more specialized treatments. General hospitals provide standard healthcare for less specialized problems. Women of low and intermediate obstetric risk can deliver in all three hospital types. Women with a high obstetric risk deliver in teaching or university hospitals.

Remifentanil patient controlled analgesia (RPCA) was first introduced as an alternative for women who had a contraindication to receive EA.[5,6] Remifentanil is a synthetic opioid with direct action on μ-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).[7] The rapid onset of analgesia (30-60 s), which peaks at 2.5 minutes[8] make remifentanil very suitable for PCA. In PCA an intravenous cannula is placed and medication is selfadministered through a PCA pump by pressing a button. The PCA device is programmed to deliver a bolus with a standard lockout time. The only opioid that is used in patient controlled analgesia in the Netherlands is remifentanil. Other opioids that are used for analgesia during labor include intramuscular meperidine and subcutaneous morphine. Efficacy of EA is superior to RPCA but studies showed comparable pain appreciation (satisfaction with analgesia).[9-10] In the Netherlands, RPCA is used frequently by women without a contra-indication for EA. An explanation might be non-availability of EA in the evening/night. This is in contrast with the recommendation of the Dutch guideline, which advises to use RPCA only in controlled (research) setting and recommends a large trial because of insufficient evidence of its efficacy and side effects and the potential risk for serious maternal complications.[1] As with EA there is large variation in the use of opioids during labor worldwide; reported numbers range from 5-66%.[11] For example, patient controlled analgesia with an opioid is available for analgesia during labor in approximately

50% of all hospitals in the UK.[12] One of the main concerns with potent opioids like remifentanil is the risk of respiratory complications (desaturation, respiratory depression). Maternal parameters should be monitored continuously in women using remifentanil and as desaturation can be a late sign of respiratory depression one to one nursing by a professional trained in basic life support is advised.[1,9]

In preparation of a randomized controlled trial comparing RPCA versus EA in labor (the RAVEL trial, NTR 2551[13]), we surveyed current practice regarding pain relief during labor. This trial has been published showing that RPCA is not equivalent to EA with respect to satisfaction with pain relief.[14]

Material and Methods

Netherlands Perinatal Registry (NPR)

Data on pregnancy, delivery and neonatal care are available in a national database; the Netherlands Perinatal Registry (NPR).[4] The NPR contains data on 97% of all births in 2010 in the Netherlands. The NPR database relies on reports of community midwives, general practitioners and obstetricians for information on all births attended. For our survey we evaluated the deliveries in the year 2010 and extracted data on the use of EA during labor. Information obtained from the NPR database were; number of women that used EA as analgesia during labor, parity, start of labor (spontaneous versus induction) and if a woman was in primary or secondary care at the start of labor. The NPR does not discriminate between different types of epidural analgesia (continuous infusion, patient controlled epidural analgesia and combined-spinal epidural analgesia). Also, only opioids as a group are registered in the database, these could be any type of opioid. Data on the use of RPCA are not available in the NPR.

Survey

A link to an anonymous online survey was sent by email to all obstetrical units of the 90 hospitals in the Netherlands with an obstetric practice. To maximize response rates the link to the survey was sent four times from August 2011 to January 2012. The survey requested data of the year 2010 on the number of deliveries and clinical management for labor analgesia. It focused on EA and RPCA for pain relief during labor. A translated version of the questionnaire can be found in appendix A. It consisted of 12 multiple choice questions with the possibility to provide additional comments. The survey addressed aspects of demography, the type of hospital (university, teaching, and general), the number of births in 2010, and percentage of births in which EA or RPCA was used. Respondents were asked about availability of EA, 24 hours a day for all women or just for a specific group, and their protocol for administration of EA (continuous infusion, patient controlled epidural analgesia, combined spinal epidural analgesia). The next part focused on the availability of RPCA, if it was available for all parturients or for a specific group of women, and on the dosage used in administration of RPCA. If RPCA was not available for all women, we asked for reasons for not offering RPCA to all women. We did not enquire about adverse events in women using

RPCA. Respondents were asked to report on actual numbers. It was decided to analyze teaching and university hospitals as one group, as university hospitals are teaching hospitals as well, and general hospitals as a separate group. Use of EA and RPCA are also reported, however, according to hospital type.

Response rate and the availability of RPCA were tested using the Chi-square test. The mean use of analgesia was analyzed using the Student's t-test. All analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Since this study does not involve human subject's ethics approval was not obtained.

Results

NPR

The total number of registered deliveries in the Netherlands in 2010 was 176,810; 26.6% of these women received analgesia (15% EA, 11.6% opioids) during labor. The other women did not receive medical pain relief during labor. Use of EA during labor was higher in nulliparous women than multiparous women (22.6% versus 7.9% (RR 2.8 95% [CI 2.8-2.9]), in women who were induced compared to spontaneous start of labor (29.1% versus 12.3% (RR 2.3 [95% CI 2.3-2.4]) and in women who started labor under supervision of an obstetrician versus women who started labor under care of a community midwife (20.4% versus 9.6% (RR 2.1 [95% CI 2.1-2.2]).

Survey

Baseline characteristics

The response rate to the survey was 67% (60). The response rate was higher for teaching and university hospitals than for general hospitals: 85% (39) versus 47% (21) ($p<0.001$) (Table 1). Not all respondents answered all non-mandatory questions in the survey. For the units responding to the survey, the mean number of deliveries in 2010 was 1718 (range 624-3050). The mean number of deliveries for teaching hospitals, including university hospitals, was 2084, for general hospitals 1039. The total of deliveries in responding hospitals was 103,097. 71% of 176,810 women delivered in secondary care in 2010. The results of our survey cover 82% of all registered births in the Netherlands.

Table 1. Overview of survey respondents according to type of hospital.

Type of hospital	Returned surveys % (n)
University hospital N=8	75 (6)
Teaching hospital N=38	87 (33)
General hospital N=44	47 (21)

Availability of pain relief

In all responding hospitals, EA was available for pain relief during labor. 95% (57) of respondents stated that EA was available 24/7 in their hospital. RPCA was available in 47% of responding hospitals, in 44% (17 of teaching hospitals and 48 (11) of general hospitals (p= 0.59). Of the 21 respondents that use RPCA in their hospital 67% (14) answered that RPCA was available for all parturients while 14% (3) used RPCA only if EA was contra-indicated. 43% (9) offered RPCA only in the last phase of the first stage, more answers were possible. Reasons for not offering RPCA to all women are listed in Table 2.

Table 2. Reasons for not using RPCA for labor analgesia or not offering RPCA to all women. More than one answer was possible.

	Obstetrician % (n) N=32
Analgesia of RPCA is insufficient, EA is the gold standard.	16 (5)
Not enough evidence for effect and side effects	38 (12)
Risk of serious side-effects like respiratory depression	44 (14)
Surveillance on labor ward is insufficient	31 (10)
Potential risks for neonate	6 (2)

Use of pain relief

The use of EA during labor varied between responding hospitals from 3% to 43% (mean 20%). Mean use of RPCA in hospitals that offered RPCA was 20% (Table 3). Comparing results of hospitals only offering EA to hospitals offering both EA and RPCA shows that in hospitals where only EA was available the use of analgesia was 20% (8-43%) while in hospitals where both were available the use of analgesia was 38% (26-63%) mean difference -17; 95% CI -22 to -12 (p<0.001).

Table 3. Percentage of deliveries in which EA or RPCA is used as analgesia.

	EA	RPCA
University hospital (mean [range])	26% [20-30]	Sporadic
Teaching hospital (mean [range])	21% [3-6]	24% [3-50]
General hospital (mean [range])	18% [5-43]	19% [13-28]

Fourteen respondents answered the questions about their protocol for RPCA. Most hospitals (86%) used a flexible background infusion of 80-100-120 µgram and 11/14 used an initial bolus dose of 30 µgram. No data were available on maximum bolus dose or lockout time.

With respect to the mode of EA most hospitals use EA with a continuous infusion (86%). But patient controlled EA and combined spinal epidural analgesia are also used in 17% and 14% respectively.

Discussion

This study was performed to evaluate the use of medical pain relief during labor in the Netherlands, with a special focus on RPCA. The results show that EA was used in 15% of all births in the Netherlands (primary and secondary care) but in 20% of births in our responding secondary care hospitals. There seems to be a large variation in the availability and use of EA and RPCA during labor between hospitals.

The difference between the uptake of EA of 15% in the NPR and the self-reported uptake of 20% in the survey is explained by the difference in denominators. The NPR reports on all births in the Netherlands, primary and secondary care combined. 28.8% of women delivered in primary care in 2010 and medical pain relief is not available in primary care. 15% of all deliveries (176.810) are 26.521 women receiving EA. 20% of all deliveries in secondary care (125.889) are 25.177 women receiving EA.

Birth is traditionally viewed by midwives and doctors in the Netherlands as a natural process where interventions are not routinely necessary and medical pain relief and interventions are seen traditionally as a last resort in difficult labor. Over the past decades we have seen increasing medicalization of pregnancy and birth, also in the Netherlands, and as a result increasing numbers of women asking for medical pain relief. Traditionally labor pain was viewed conservatively as a normal physiological phenomenon that serves a purpose (increasing bond between mother and child). Nowadays, more and more women view labor pain as unnecessary, and because of this are more likely to request medical pain relief during labor. In this article we discuss the use of analgesia in the year 2010. The number of women using EA has been increasing with 1-2% per year in the past years and was 20% in 2014.

Despite recommendations of the guideline to use RPCA only in a controlled (research) setting, RPCA is used in almost 50% of responding hospitals and in only 14% reserved for women with a contra-indication for EA. We found that the use of analgesia during labor seems significantly higher in hospitals that offer both EA and RPCA than use of analgesia in hospitals that offer only EA. In hospitals that use RPCA as well as EA for pain relief during labor, EA is used in approximately 20% of all deliveries (range 3-43%), equal to hospitals that do not offer RPCA, and RPCA is used in a little over 20% additional deliveries in these hospitals (range 3-50%). The higher uptake of analgesia in hospitals that use RPCA could suggest that in these hospitals RPCA is not used as an alternative to EA but may be used in addition to other methods of pain relief that are available

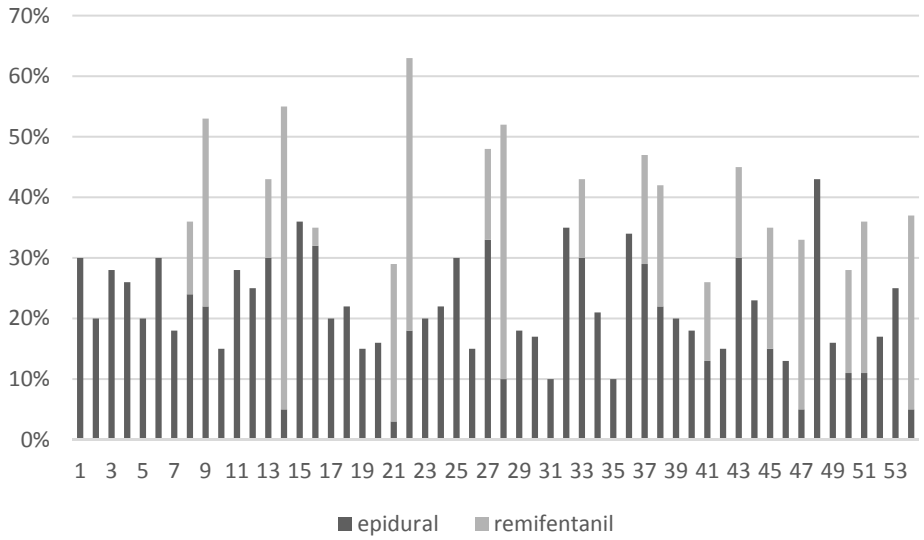

Figure 1. Percentage of pain relief according to center.

There could be several reasons for a higher use of pain relief in hospitals that offer both EA and RPCA. The first is the perception of women and/or caretakers (community midwives/ obstetricians) that RPCA is a less invasive method of pain relief than EA, because only intravenous access is required. Hence, women who are reluctant to ask for EA could be more likely to request RPCA. A second reason could be that women who are expected to give birth within a relatively short period of time are given RPCA when they request pain relief at this stage of labor. These are women who are expected to deliver soon and who might be too late to receive EA. This theory is supported by the findings of Logtenberg et al., who found a significant larger number of multiparous women receiving analgesia when randomized to RPCA (unpublished data). Another explanation could be that RPCA is more easily available than EA for women asking for pain relief because the presence of an anesthesiologist is not required. The decision to start RPCA is made by the obstetrician or clinical midwife in most Dutch hospitals and not all hospitals require presence of an anesthesiologist at the start of RPCA. It is not likely that the higher use of pain relief in hospitals that offer both EA and RPCA is explained by a different population of parturients, e.g. higher risk deliveries, since RPCA is used most in teaching and general hospitals but not in university hospitals (which have the highest risk population). The last explanation for this difference is response bias, because not all units responded to our questionnaire it is possible we got response from the units with a higher uptake of analgesia.

Little is known about the percentages of births in which RPCA is used worldwide. To our knowledge three surveys addressed this.[12,15,16] So it is difficult to know whether our findings are generalizable to the situation in other countries. In the UK PCA with an opioid was used in almost 50% of responding units in 2004-2005, in 35% of those remifentanil was used. In Germany PCA with an opioid was used in 8% of responding units with the use of remifentanil in 68%. In the French part of Belgium

36% of respondents use PCA in their unit and 77% of those use remifentanil as the opioid of choice. Comparing our findings and previous reports, the use of EA and the use of patient controlled analgesia seem comparable in the Netherlands, the UK and Belgium.[11,12] Our survey only asked about remifentanil PCA. To our knowledge no other opioids are used for PCA in the Netherlands and following the results of Douma et al., remifentanil provides better analgesia than fentanyl or meperidine through PCA.[17]

Strengths and limitations

The main strength of this study is that it is one of only a few studies reporting on the use of RPCA as analgesia during labor.

A weakness is the response rate. Our overall response rate was acceptable with a response of 67%: high for teaching hospitals (87%) but low for general hospitals (47%). Since the response rate of teaching hospitals, which are the bigger centers, was 87%, we believe the results give a representative view of practice and beliefs regarding pain relief during labor in the Netherlands.

Conclusion

In the Netherlands, there is large variation in the availability and use of EA and RPCA during labor. Despite recommendations of the guideline to use EA as analgesia of first choice and RPCA only in a controlled (research) setting, RPCA is used in almost 50% of hospitals and offered to all women in 67% of those.

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Remifentanil patient controlled analgesia versus epidural analgesia in labour. A multicentre randomized controlled trial

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Abstract

Background: Pain relief during labour is a topic of major interest in the Netherlands. Epidural analgesia is considered to be the most effective method of pain relief and recommended as first choice. However its uptake by pregnant women is limited compared to other western countries, partly as a result of non-availability due to logistic problems. Remifentanil, a synthetic opioid, is very suitable for patient controlled analgesia. Recent studies show that epidural analgesia is superior to remifentanil patient controlled analgesia in terms of pain intensity score; however there was no difference in satisfaction with pain relief between both treatments.

Methods/design: The proposed study is a multicentre randomised controlled study that assesses the cost-effectiveness of remifentanil patient controlled analgesia compared to epidural analgesia. We hypothesize that remifentanil patient controlled analgesia is as effective in improving pain appreciation scores as epidural analgesia, with lower costs and easier achievement of 24 hours availability of pain relief for women in labour and efficient pain relief for those with a contraindication for epidural analgesia.
Eligible women will be informed about the study and randomised before active labour has started. Women will be randomly allocated to a strategy based on epidural analgesia or on remifentanil patient controlled analgesia when they request pain relief during labour. Primary outcome is the pain appreciation score, i.e. satisfaction with pain relief.
Secondary outcome parameters are costs, patient satisfaction, pain scores (pain-intensity), mode of delivery and maternal and neonatal side effects.
The economic analysis will be performed from a short-term healthcare perspective. For both strategies the cost of perinatal care for mother and child, starting at the onset of labour and ending ten days after delivery, will be registered and compared.

Discussion: This study, considering cost effectiveness of remifentanil as first choice analgesia versus epidural analgesia, could strongly improve the care for 180.000 women, giving birth in the Netherlands yearly by giving them access to pain relief during labour, 24 hours a day.

Keywords
Analgesia, labour, remifentanil, patient controlled analgesia, epidural.

Background

Epidural analgesia is considered to be the most effective method of pain relief during labour and is recommended as first method of pain relief by the Dutch Societies of Gynaecologists and Anesthetists.[1,2] In the Netherlands its uptake by pregnant women in labour of all ethnicities is still limited (11.3% in 2008 but in the last years increasing with 1-2% per year), compared with other western countries, partly as a result of non-availability due to logistic problems. This is an undesirable situation, especially since the number of women asking for pain relief during labour is increasing. There is also need for a safe alternative for women who cannot receive epidural analgesia because of contraindication for epidural analgesia.

The availability and uptake of epidural analgesia during labour varies significantly between countries, for example approximately 20% of women in the UK and 58% of women in the USA use this form of pain relief. There is considerable variation in the availability of epidural analgesia within the UK as in the Netherlands.[3]

There are situations in which epidural analgesia is contra-indicated. In these cases intramuscular or intravenous opioids provide an alternative. Variation is also present in the use of opioids during labour, reported numbers range from 5-66%. In the last update of the Cochrane review "Parenteral opioids for maternal pain management in labour" the authors recommend a pragmatic large randomized controlled trial to compare pain relief using an opioid to other methods of pain relief to collect data on maternal satisfaction, co-interventions and maternal and neonatal outcome prospectively.[4]

At present in the Netherlands, pain relief during labour is of major interest and an important topic for pregnant women, health care providers and politicians, as is pointed out in the publication of the Steering Committee Pregnancy and Birth installed by the Dutch Ministry of Health, Welfare and Sports.[3] One of the advices is that all Dutch women in labour should have access to adequate pain relief. The working party of the Dutch guideline "Pain relief during labour" recommends using remifentanil patient controlled analgesia (PCA) only in controlled setting and recommends a large trial. Nevertheless, over one third of Dutch hospitals use remifentanil PCA on labour wards. Possible explanations are that the presence of an anaesthetist for this type of analgesia is not required and that administration of remifentanil is quicker and less invasive than epidural analgesia. Literature study reveals that this does not only apply to the Dutch obstetrical system, which differs from other western countries because of a higher percentage of women under the care of community midwives and of home-births.

The most commonly used opioid is intramuscular pethidine. However, its analgesic effectiveness is widely challenged.[5-7] Remifentanil is a synthetic opioid (anilidopiperidine) with direct agonist action specifically on μ-opioid receptors.[8] The rapid onset and offset of the drug make remifentanil very suitable for administration via patient controlled analgesia (PCA), which can be used for analgesia during labour. Placental transfer of remifentanil does occur but appears to be rapidly metabolised, redistributed, or both. There were no adverse neonatal or maternal effects, only mild maternal sedation and respiratory changes.[9] There have been multiple clinical studies on the use of remifentanil in women in labour.[10-22]

Two studies address pain relief scores of remifentanil PCA (patient controlled analgesia) compared to epidural analgesia, although both had limitations. Volmanen et al. limited the observation period to only one hour. Douma et al. recorded pain relief scores as a secondary outcome measure in a study powered to investigate difference in pain scores. Both studies showed that in terms of pain scores (pain-intensity), epidural analgesia is superior to remifentanil PCA. However, there was no difference in the pain appreciation scores between both treatments.[23,24]

Methods/Design

Aims

The objective of this study is to test the hypothesis that remifentanil PCA is as effective as epidural analgesia with respect to patient satisfaction and pain appreciation scores, with lower costs and possibly the benefit of easier achievement of 24 hours availability of pain relief for women in labour.

Participants/eligibility criteria

All pregnant women in the participating hospitals will be informed of the trial at antenatal visits in the third trimester. They can participate in the trial if they are healthy or have a mild systemic disease (ASA physical status 1 or 2) and are 18 years or older with a gestational age >32 weeks. Randomisation takes place before active labour has started, at antenatal visits in the third trimester or at admission on the ward before induction. Exclusion criteria are hypersensitivity for any of the products used or if there is a contraindication for epidural analgesia.

Procedures, recruitment, randomisation, collection of baseline data

The study will be a multicentre randomised controlled study. The study will be performed within the Dutch Consortium for Studies in Women's Health and Reproductivity. Participating hospitals can be district, teaching or third referral hospitals. Before entry into the study, women are informed about the aims, methods, reasonably anticipated benefits and potential hazards of the study. They are informed that their participation is voluntary and that they may withdraw consent to participate at any time during the study. Choosing not to participate will not affect care. In every centre an independent gynaecologist will be available for more detailed information both for patients and colleagues if required.

After giving sufficient information, written informed consent is obtained. The consent form must be signed before performance of any study-related activity. After obtaining informed consent women will be randomised and will be informed on the assigned method of pain relief before labour starts (as in usual care). They are only given pain relief during labour at their request or if a medical reason should arise.

Randomisation will be stratified for centre and parity. We will apply block randomization with a fixed block size. Randomisation will be performed through a web-based database located in the central data collection unit in the AMC in Amsterdam. Women will be randomly allocated to receive remifentanil PCA or epidural analgesia when they request pain relief during labour. There will be no

blinding, as this is not possible due to the nature of the two treatment methods.

Baseline demographic, past obstetric and medical histories, including ASA physical status, will be recorded for all women.
All details of delivery and health care received in the ten days after delivery are recorded in the case record form that is accessible through a website http://www.studies-obsgyn.nl/ravel.

Interventions

After giving informed consent women will be randomised to receive remifentanil PCA or epidural analgesia during labour if they request pain relief during labour. Parturients randomised to intravenous remifentanil will receive a 30 µg loading dose and boluses of 30 µg with a 3 minute lockout time. We decided on a flexible bolus dose. In case of insufficient pain relief the bolus can be increased to 40 µg or decreased to 20 µg in case of excessive side effects. Parturients randomised to epidural analgesia will receive epidural analgesia according to local protocol.

Outcome measures

The main outcome parameter is pain appreciation, i.e. satisfaction with pain relief. Women will be asked to express their level of satisfaction with pain relief every 15 min during the first hour and hourly after that. This will be scored on a visual analogue scale (VAS) ranging from 1 (highly dissatisfied) to 10 (highly satisfied).
Secondary endpoints are pain scores, scored on a visual analogue scale ranging from 1 (no pain) to 10 (worst imaginable pain), maternal side effects, mode of delivery and maternal and neonatal mortality and morbidity.

Economic evaluation

General consideration

The results of the study will provide insight on whether remifentanil PCA in women in labour will reduce costs as compared to epidural analgesia, assuming there will be equivalence in pain appreciation of both methods. At present, no clinical study has been published or undertaken to investigate this issue. An estimation of costs for remifentanil PCA versus epidural analgesia shows a decrease of 64 euro per patient. The difference in costs is due to the extra costs of anaesthetic staff and nurses, required when epidural analgesia is given.

Cost analysis

The economic analysis will be performed from a short-term healthcare perspective. Anticipating on equality in pain appreciation scores the economic analysis will be a cost minimization analysis. For both strategies the cost of perinatal care for mother and child, starting at the onset of labour and ending ten days after delivery, will be registered and compared (without discounting). The costs consist of costs of delivery/childbirth (course and mode of delivery), postnatal maternal care (hospitalization, outpatient visits), neonatal care (admission to NICU/neonatology ward, outpatient

visits) and primary care (midwife, general practitioner, maternity care).
Volumes of hospital care are measured prospectively alongside the clinical study in all participating centres as part of the case record form. Health resource use outside the hospital will be recorded by questionnaires filled out by the patients. Costs of delivery/childbirth will be based on cost price analysis. Other resource use (hospital days, outpatient visits and primary care) will be valued using standard prices.[25]

Follow up of women and infants

Details of admission of women and newborns will be recorded as will maternal and neonatal complications. Long term follow up is at present not part of this study.

Statistical issues

Sample size

The sample size is calculated based on the primary outcome measure pain appreciation. We hypothesize that there is no difference in pain appreciation with the two sided test (alfa=0.05, power (1-beta=0.9)). In this non-inferiority design in each group 102 women have to be treated to exclude a potential clinical relevant difference of 10% (10 point scale, estimated SD 2.2). Allowing for 10% and 30% cross-over/non-compliance in the control group and experimental group respectively, 568 patients are required. We estimate that in the group of pregnant women who are willing to participate in the study 50% will actually need pain relief. This in contrast to the whole Dutch pregnant population, which is known for a low uptake of pain relief during labour. Therefore 1136 women have to be randomised. In case of missing data on the primary endpoint, we will extend the number of women to be recruited accordingly.

Data analysis

Data will be analysed according the intention to treat principle. First, the remifentanil and epidural group will be compared. Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures. Categorical variables will be tested with the Chi-square test or Fisher's exact test. Continuous variables will be tested with the Mann-Whitney U test. Time to delivery will be assessed using Kaplan-Meier analysis. In case of equivalence between outcomes, the analysis will be repeated on a par protocol basis. Subsequently, planned subgroup analysis will be done for nulliparous versus parous women, previous caesarean section, preterm labour (32-34 weeks and 34-37 weeks) and term labour (37-42 weeks), spontaneous versus induced labour, maternal educational level, maternal age (under 35 years versus over 35 years) and multiple pregnancy. We will then use decision analysis to evaluate which intervention strategy, i.e. remifentanil or epidural analgesia is preferred in women who need analgesia during labour.

Interim analysis

No interim analysis will be performed. Because of the suggested design of the trial where equivalence is expected all 1136 women have to be randomized in order to achieve sufficient power. Both remifentanil PCA and epidural analgesia are widely used in the Netherlands as pain relief during labour and no adverse events have been recorded to date.

Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to a Data Safety Monitoring Committee (DSMC). The DSMC can order to perform an interim analysis and, if indicated, terminate the trial prematurely.

Ethical considerations

This study is approved by the National Central Committee on Research involving Human Subjects (CCMO - NL34262.058.10.), by the ethics committee of the Leiden University Medical Centre (Ref. No. P10-240) and by the boards of management and ethics committees of all participating hospitals.

Discussion

In the Netherlands uptake of epidural analgesia is lower than in surrounding western European countries. This can be partly due to our obstetrical system; a large number of women under the care of community midwives and about 25% of all births take place at home. Epidural analgesia is recommended as first method of pain relief by the Dutch Societies of Gynecologists and Anesthetists. In daily practice not every labour ward in the Netherlands has 24 hour availability of epidural analgesia. One of the alternatives is remifentanil PCA. Over one third of all hospitals use remifentanil as pain relief during labour. With this study we aim to test the hypothesis that remifentanil PCA and epidural analgesia are equivalent in pain appreciation with possible fewer costs. The outcome of this study could improve the care for over 180.000 women giving birth in the Netherlands yearly.

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4

Remifentanil patient controlled analgesia versus epidural analgesia in labour; a randomised multicentre equivalence trial

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Abstract

Objective: To determine women's satisfaction with pain relief using patient controlled analgesia with remifentanil compared with epidural analgesia during labour.

Design: Multicentre randomised controlled equivalence trial.

Setting: 15 hospitals in the Netherlands.

Participants: Women with an intermediate to high obstetric risk with an intention to deliver vaginally. To exclude a clinically relevant difference in satisfaction with pain relief of more than 10%, we needed to include 1136 women. Because of missing values for satisfaction this number was increased to 1400 before any analysis. We used multiple imputation to correct for missing data.

Intervention: Before the onset of active labour consenting women were randomised to a pain relief strategy with patient controlled remifentanil or epidural analgesia if they requested pain relief during labour.

Main outcome measures: Primary outcome was satisfaction with pain relief, measured hourly on a visual analogue scale and expressed as area under the curve (AUC), thus providing a time weighted measure of total satisfaction with pain relief. A higher AUC represents higher satisfaction with pain relief. Secondary outcomes were pain intensity scores, mode of delivery, and maternal and neonatal outcomes. Analysis was done by intention to treat. The study was defined as an equivalence study for the primary outcome.

Results: 1414 women were randomised, of whom 709 were allocated to patient controlled remifentanil and 705 to epidural analgesia. Baseline characteristics were comparable. Pain relief was ultimately used in 65% (447/687) in the remifentanil group and 52% (347/671 in the epidural analgesia group (relative risk 1.32, 95% confidence interval 1.18 to 1.48). Cross over occurred in 7% (45/687) and 8% (51/671) of women, respectively. Of women primarily treated with remifentanil, 13% (53/402) converted to epidural analgesia, while in women primarily treated with epidural analgesia 1% (3/296) converted to remifentanil. The area under the curve for total satisfaction with pain relief was 30.9 in the remifentanil group versus 33.7 in the epidural analgesia group (mean difference −2.8, 95% confidence interval −6.9 to 1.3). For who actually received pain relief the area under the curve for satisfaction with pain relief after the start of pain relief was 25.6 in the remifentanil group versus 36.1 in the epidural analgesia group (mean difference −10.4, −13.9 to −7.0). The rate of caesarean section was 15% in both groups. Oxygen saturation was significantly lower (SpO_2 <92%) in women who used remifentanil (relative risk 1.5, 1.4 to 1.7). Maternal and neonatal outcomes were comparable between both groups.

Conclusion: 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.

Introduction

Epidural analgesia is considered to be the most effective method of pain relief during labour and is often the preferred choice of analgesia.[1] Intramuscular or intravenous opioids can provide an alternative in situations where regional analgesia is unavailable or contraindicated or if less invasive methods are preferred by the woman or obstetrician.[2] Remifentanil is a potent μ-opioid receptor agonist. Its short context sensitive half life (3-4 minutes) and short elimination half time (10-20 minutes) make it suitable for administration under the control of the patient for women in labour who want pain relief.[3] Placental transfer of remifentanil occurs, but the opioid is rapidly metabolised and redistributed by the fetus.[4]

Although epidural analgesia during labour is the preferred method because it provides superior analgesia to systemic opioids, various studies show comparable maternal satisfaction with patient controlled remifentanil.[5,6] Two previous studies that assessed satisfaction with pain relief with patient controlled remifentanil compared with 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,[5] while Douma and colleagues recorded pain relief scores as a secondary outcome in a study powered to investigate difference in pain scores.[6] In both studies, epidural analgesia was superior to patient controlled remifentanil in terms of pain intensity.

The most recent Cochrane review on this topic recommended a randomised controlled trial to examine patient controlled analgesia with an opioid compared with other methods of analgesia and to report on maternal satisfaction, co-interventions, and maternal and neonatal outcomes.[7] We conducted this study to test the hypothesis that patient controlled remifentanil is equivalent to epidural analgesia with respect to satisfaction with pain relief.

Methods

Design

We performed a multicentre randomised clinical trial within the Dutch consortium for women's health and reproductivity (NTR 2551). The study was performed in three academic hospitals, 11 teaching hospitals, and one general hospital. In the Netherlands healthy low risk pregnant women start antenatal care in primary midwifery led care. When medical complications occur, either maternal or fetal, women are referred to secondary or tertiary care. For this study we recruited only women in secondary and tertiary care (intermediate/high risk). Women are considered low risk if their medical and/or obstetric history is uneventful. Women are considered intermediate or high risk if they have illnesses in their medical history that can affect pregnancy or that are affected by pregnancy or if they have complications in this or previous pregnancies or deliveries.

Women were eligible to participate if they were healthy or had a mild systemic disease (American Society of Anesthesiologists physical classification 1 or 2),[8] were aged 18 or older, and were scheduled to deliver vaginally after 32 weeks. Exclusion criteria were contraindications for epidural analgesia or hypersensitivity to one of the drugs used.

After informed consent, but before the onset of active labour, women were randomly allocated to patient controlled remifentanil or epidural analgesia. All women were randomised before the start of actual labour. As analgesia during labour was given only if it was requested, not all women received pain relief.

Interventions

Remifentanil group

The patient controlled device was programmed to deliver 30 µg remifentanil (solution 20 µg/mL) on request with a lockout time of three minutes. This dose regimen was based on previous studies.[6,9] The dose could be increased to 40 µg in case of insufficient pain relief or decreased to 20 µg in case of excessive side effects. No background infusion was allowed. Women who were treated patient controlled remifentanil were instructed on how to use the device and to maximise analgesia by pressing the device's button in anticipation of the next contraction. Remifentanil has a rapid onset of action and short context sensitive half life, thus administration of a bolus dose in anticipation of the next contraction ensures maximum effect.[3] If pain relief was inadequate, women could request epidural analgesia. They were advised to discontinue using the device during the second stage of labour to minimise the risk of neonatal side effects.

Epidural analgesia group

Women randomised to epidural analgesia received this when they requested pain relief, according to local protocol. If pain relief after epidural analgesia was judged inadequate by the woman, she could receive patient controlled remifentanil instead of epidural analgesia. No advice was given regarding continuing epidural analgesia during the second stage of labour. Dutch guidelines advise the continuation of epidural analgesia during second stage provided there is no effect on motor function.[1]

Data collection

During labour, women were asked two separate questions. They were asked to rate their satisfaction with pain on a self-designed ruler with a visual analogue scale ranging from 0 (highly dissatisfied) to 100 mm (highly satisfied). They started from the beginning of actual labour and were asked to report hourly. In addition, they were asked to rate the pain intensity score during contractions every hour on a scale ranging from 0 (no pain) to 100 mm (worst pain imaginable).

For satisfaction with pain relief, women were asked to rate their satisfaction with pain (relief) ("how would you rate your satisfaction with pain relief?") on a visual analogue scale. This was described briefly in the patient information before randomisation and in detail at admission for delivery. For the pain intensity score, women asked to rate their pain score ("how would you rate your pain during a contraction?") on a different visual analogue scale.

Written examples of these questions and how to use the VAS ruler were available at the labour ward (see appendix 1). After birth, women were asked to rate their overall satisfaction with the pain during labour on an 11 point numerical rating scale as a measure of the overall pain experience. They were not asked to rate the overall experience of labour.

Maternal oxygen saturation was monitored continuously in women receiving pain relief. The following measurements were obtained and recorded once before the start of analgesia and at 15 minute intervals during the first hour of treatment followed by hourly recordings until delivery: maternal temperature, blood pressure, heart rate and respiratory rate, and oxygen saturation determined by pulse oximetry.

In women who received analgesia, the nurse, midwife, or obstetrician recorded the incidence of nausea, vomiting, itching, hypotension (systolic blood pressure <90 mm Hg), desaturation (SpO_2 <92%), and respiratory depression (frequency <8/min). Additional measures were advised in case of hypotension, maternal desaturation, or respiratory depression.

Fetal heart rate and uterine activity were measured with external fetal cardiotocography or fetal scalp electrode and intrauterine pressure device.

Outcomes

The primary outcome measure was satisfaction with pain relief measured on a visual analogue scale ranging from 0-100 mm. Satisfaction was expressed as the area under the pain satisfaction curve, which is a summary measure that integrates serial assessments of a woman's satisfaction with pain relief over the duration of the study. The area under the curve (AUC) is a measure that is often used in clinical pharmacology, but it can also be used for clinical endpoints—for example, the use in pain assessment.[10-13] A higher AUC represents a higher satisfaction with pain relief. The AUC was calculated for the duration of labour and for the time that pain relief was administered. The AUC could be calculated if a woman had rated satisfaction with pain relief on at least two different time points.

Our published protocol stated that both effectiveness and cost effectiveness were primary outcome measures. Satisfaction with pain relief was the primary outcome measure for effectiveness from the start of the study. We planned to perform a cost effectiveness analysis as well, taking into account the primary outcome for effectiveness. Because this was not made clear enough in the original protocol and registry it was changed in the last amended protocol. This last amended protocol was submitted before the last randomised woman delivered and as a result we did not have access to the data.[14]

Secondary outcome measures were the AUC for pain intensity scores, score for overall satisfaction with pain relief during labour, the highest pain intensity score during labour, pain intensity and satisfaction with pain relief at the moment of request for pain relief, highest score for satisfaction with pain relief after pain relief was used, and the mean scores of pain and satisfaction with pain relief.

We also recorded characteristics of labour (time from request to start of analgesia, duration of analgesia, duration of second stage, use of oxytocin, mode of delivery, reasons for instrumental delivery), maternal outcomes (postpartum haemorrhage (estimated blood loss >1000 mL), suspicion of intrapartum infection (temperature >38.0°C and the use of antibiotics), spinal headache, major maternal complications, maternal parameters (temperature, blood pressure, oxygen saturation, and respiratory rate)), and maternal admission. For the neonate we assessed Apgar score at 5 minutes, arterial cord blood pH, neonatal admission, and reasons for neonatal admission.

Sample size calculation

We calculated our sample size based on the primary outcome measure of satisfaction with pain relief, assuming that there would be no difference in satisfaction (two sided test, α 0.05, power 0.9). In this equivalence design, we would need 102 women to be treated in each group to exclude a potential clinically relevant difference of 10% (on an 11 point scale, estimated SD 2.2). Allowing for 30% and 10% cross over in the remifentanil group and epidural analgesia group, respectively, we needed 568 women in total. We estimated that out of pregnant women who would be willing to participate in the study, about 50% would actually request analgesia. We therefore needed to randomise 1136 women. In anticipation of missing data on the primary endpoint during the study period, we extended the number of women to 1400 before any comparative analysis. This sample size was calculated based on a visual analogue scale for satisfaction with pain relief at one time point. In February 2013 we amended the protocol because we decided to change the primary outcome from a score at one time point to the area under the satisfaction curve, which integrates all visual analogue scores measured over time. In our opinion the AUC best represents the overall satisfaction with pain relief and it can deal with missing values, but at the start of the trial we were not well enough aware of this.

For this measure we also judged that 10% equals a clinically relevant difference. Our sample size calculation was done on a different outcome parameter. In the sample size calculations, we used 10% reduction on the visual analogue scale for satisfaction with pain relief as equivalence margin, which is one point reduction in satisfaction with pain relief. As we changed the primary outcome measure to a time weighted measure by using the AUC, we could no longer use this equivalence margin. We therefore used an equivalence margin of 10% of the mean AUC.

Interim analysis and stopping rules

We used specially designed forms to report serious adverse events and suspected unexpected serious adverse reactions to the ethics committee of the Leiden University Medical Centre. A data safety monitoring board was established before the start of the trial. No interim analysis was performed because of the equivalence design of the trial. Serious adverse events and reactions were reported to the board and medical ethics committee to evaluate the safety of women. Predefined serious adverse events were requirement for mechanical ventilation or cardiopulmonary resuscitation, meningitis, and epidural haematoma. Apart from that we asked to be informed about respiratory depression <8 breaths/minute and oxygen saturation <92% that did not respond to a decrease in bolus dose. These events had to be reported to the principal investigator and to the data safety monitoring board. If deemed necessary the data safety monitoring board would be able to (temporarily) stop the study.

Randomisation and blinding

Randomisation was performed through a web based randomisation program. We randomised in fixed blocks of three, stratified for centre and parity. The allocation code appeared after a patient's initials were entered into the randomisation program.

All women were randomised before the start of labour. If women requested pain relief during labour, the allocated intervention was provided. Women did not have the option of choosing analgesia other than according to randomisation. Blinding was not possible because of the nature of the two interventions. Research nurses/midwives as well as attending medical staff performed randomisation.

Data analysis

The trial was designed as an equivalence trial for the primary outcome measure AUC of satisfaction with pain relief and the secondary outcome measure AUC of pain intensity. The other secondary outcomes were analysed for superiority. Our null hypothesis was that the difference in the score for satisfaction with pain relief, scored on a visual analogue scale (0-100 mm), between the two study groups would be greater than 10%. Preliminary unpublished data in perioperative patients using patient controlled opioid treatment had shown that changes (that is, increases) in pain intensity scores of 10% or larger will prompt action in a patient—that is, he or she will require additional pain relief by pressing the device's button. Extrapolation of these data to the current study suggests that at differences in visual analogue scores of 10% or more, clinical differences in satisfaction with pain relief can be assumed. We calculated the estimated standard deviation using data from Volmanen and colleagues[5] and converted those from a five point to an 11 point scale. Data were analysed on an intention to treat basis. We tested for equivalence by determining whether the upper and lower limits of the two sided 95% confidence interval on the primary endpoint AUC of satisfaction with pain relief and the secondary endpoint AUC of pain intensity did not exceed the equivalence margin of 10%. Normally distributed data were presented as means with SDs; skewed distributions were presented as medians with interquartile range. For categorical data, the treatment effect was presented as relative risk with 95% confidence intervals. For secondary outcome measures we calculated P values with the χ^2 test, unless the expected cell count was less than 5, in which case we used the Fisher's exact test. For continuous data with a non-normal distribution, we used the Mann-Whitney U test.

Calculation of the percentages was based on the number of valid observations. Statistical analysis was performed with SPSS version 20 (SPSS, Chicago, IL). $P<0.05$ was considered significant.

We performed two analyses. Firstly, we analysed the whole group of randomised women on an intention to treat basis. This analysis included women who did and did not receive any pain relief (687 in remifentanil group, 671 in epidural group). In a second analysis, we included only those women who actually received pain relief (447 in remifentanil group, 347 in epidural group). To correct for possible confounding in the second analysis because a larger number of women who received pain relief were in the group allocated to remifentanil, we also compared the two randomisation groups in the subgroup of women who actually received pain relief using multiple linear regression, with adjustment for randomisation outcome, age, race, education, parity, onset of labour, dilation at request of pain relief, and premature labour.

Subgroup analyses

We planned subgroup analyses for satisfaction with pain relief for nulliparous women versus multiparous women, previous caesarean section, spontaneous versus induced labour, educational level, aged under 36 versus 36 or older, gestational age at delivery (<34 weeks, 34-37 weeks, >37 weeks), and singleton versus multiple pregnancy.

Missing data

We used multiple imputation with SPSS to correct for missing primary outcome data.[15-17] We imputed missing AUC values for satisfaction with pain relief and pain intensity (transformed so that the distribution was approximately normal) using 20 imputed datasets. Other missing values were not imputed.

Results

Between 30 May 2011 and 24 October 2012, we randomised 1414 women to receive patient controlled remifentanil (n=709) or epidural analgesia (n=705) should they request analgesia during labour. After randomisation, we excluded 51 women (22 in remifentanil group, 29 in epidural group) because of elective caesarean section.

In the epidural group, three women were lost to follow-up, while two withdrew informed consent after randomisation. We analysed the data from 1358 women, 687 in the remifentanil group and 671 in the epidural group (figure 1). Baseline characteristics were comparable between groups (table 1).

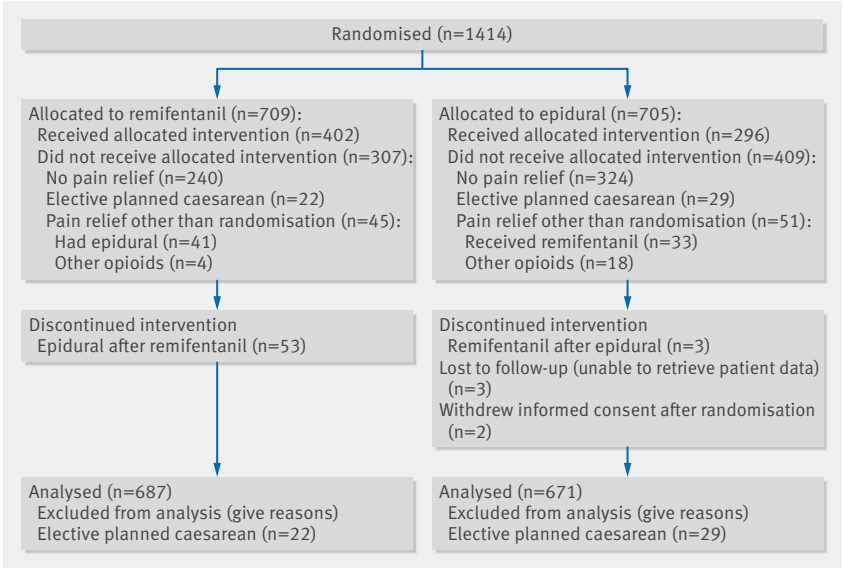

Figure 1. Randomisation and flow of pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour

Table 1. Baseline characteristics of pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour. Figures are numbers (percentage) unless otherwise indicated

	Remifentanil (n=687)	Epidural analgesia (n=671)
Median (IQR) gestational age at randomisation (weeks)	37.8 (35.5-39.2)	37.1 (35.3-39.0)
Mean (SD) maternal age (years)	31.5 (5.1)	31.7 (4.8)
White ethnic origin	579 (88)*	561 (90)†
Education ≥higher	281 (52)‡	296 (55)§
Median (IQR) BMI	23.7 (21.5-26.9)¶	23.8 (21.4-27.6)**
ASA classification:		
1	491 (72)	461 (69)
2	196 (29)	210 (31)
Parity:		
0	323 (47)	329 (49)
≥1	364 (53)	342 (51)
Multiple pregnancy	24 (4)	30 (5)

IQR=interquartile range; BMI=body mass index; ASA=American Society of Anesthesiologists.
*4.2% (29) missing. †6.4% (43) missing.‡21.7% (149) missing. §20.4% (137) missing. ¶8.9% (61) missing. **11.0% (74) missing.

Of the 709 women randomised to patient controlled remifentanil, 447 (65%) actually received analgesia during labour, compared with 52% (347) in the epidural analgesia group (relative risk 1.32, 95% confidence interval 1.18 to 1.48). Of the 447 women in the remifentanil group who received pain relief, 402 women received immediate remifentanil. 45 women received other analgesia than allocated to; 41 received epidural analgesia, and four received other opioids. Of the 402 women who started remifentanil, 53 women converted to epidural analgesia because of insufficient analgesia (figure 1). Of women who were treated with remifentanil, 92% (411/447) started with a dose of 30 µg; the other women were given an initial dose of 20-40 µgr. In 13% (59/447) the dose was increased once, and in 3% (14/447) it was decreased once. In 3% (12/447) and 0.7% (3/447) the bolus dose was increased twice or three times, respectively. Of the 347 women who requested pain relief and been allocated to epidural analgesia, 296 received immediate epidural analgesia. 51 women were received other analgesia than allocated to; 33 were treated with remifentanil (of whom two women converted back to epidural analgesia after remifentanil), and 18 received other opioids. Three women initially treated with epidural analgesia converted to remifentanil because of insufficient analgesia (figure 1).

The epidural regimens used were ropivacaine/sufentanil (37%), bupivacaine/sufentanil (46%), levobupivacaine/sufentanil (6%), and bupivacaine/fentanyl (11%).

Reasons for non-compliance (treatment other than the randomised outcome) included doctors' or patients' preference/request, expectation of quick or slow delivery, logistical problems (for instance, non-availability of the anaesthetist (within one hour)), and new contraindication for randomised treatment (table 2).

Table 2. Pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour who received the other measured intervention

	Randomised to epidural analgesia, received remifentanil (n=33)	Randomised to remifentanil, received epidural analgesia (n=41)
Patient demand	7	25
Physician assessment	11	9
Contraindication for randomised treatment	3*	3†
Logistical problems	9	1
Technical difficulties	3	0
Unknown/missing	0	3

*Family history of Rendu-Osler-Weber syndrome, aortic valve stenosis, HELLP syndrome with thrombocyte count of 36.
†Opioids administered <6 hours, initial maternal SpO_2 <95%, initial maternal temperature >38° C.

Missing data

We could calculate the primary outcome measure, AUC for satisfaction with pain relief during active labour, for 57% of women in the remifentanil group and 43% in the epidural group. In the subgroup of women who received analgesia, the AUC for satisfaction with pain relief during administration of pain relief could be calculated for 71% and 57%, respectively.

The AUC for pain intensity score during active labour could be calculated for 64% of participants in the remifentanil group and 53% in the epidural group. In the subgroup of women who received analgesia the AUC for pain intensity score could be calculated for 77% of women in the remifentanil group and 63% in the epidural group. Characteristics of complete and incomplete cases are in appendix 2.

Primary outcome

The AUC for satisfaction with pain relief during labour for all randomised women was lower in the remifentanil group (difference −2.8, 95% confidence interval −6.9 to 1.3). As this does not exclude a potential clinically relevant difference, we cannot conclude that the treatments are equivalent. Furthermore, in the subgroup of women who actually received analgesia, the AUC for satisfaction with pain relief after start of pain relief was significantly lower in women who asked for pain relief and were randomised to remifentanil (difference −10.4, −13.9 to −7.0) (table 3).

The AUC for pain intensity during labour for all randomised women was higher in the remifentanil group (difference 3.8, 95% confidence interval 0.92 to 6.6). For the group of women who actually received analgesia, the AUC for pain intensity after the start of pain relief was significantly higher in women who requested pain relief and were randomised to remifentanil (difference 6.4, 3.5 to 9.4) (table 3).

Table 3 also shows the values without imputation for the AUC, providing a larger effect size than the imputed values. Results of the comparisons in the group of women who actually received analgesia, with adjustment for possible confounders, were similar: the difference in AUC for satisfaction with

pain relief after the start pain relief was −8.7 (95% confidence interval −12.0 to −5.5) and the difference in AUC for pain score after the start pain relief was 7.6 (4.8 to 10.4).

Table 3. Area under curve for satisfaction with pain relief and pain scores during active labour and after start pain relief in pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour.

	Mean area under curve		
Measure (No of women per group)	**Remifentanil**	**Epidural analgesia**	**Difference (95% CI)**
With missing AUC values imputed			
Satisfaction with pain relief during active labour (687/671)	30.9	33.7	−2.8 (−6.9 to 1.3)
Satisfaction with pain relief after pain relief (447/347*)	25.6	36.1	−10.4 (−13.9 to −7.0)
Pain during active labour (687/671)	30.9	27.2	3.8 (0.92 to 6.6)
Pain score after pain relief (447/347*)	26.7	20.3	6.4 (3.5 to 9.4)
Missing AUC values not imputed			
Satisfaction with pain relief during active labour (394/290)	27.2	37.6	−10.3 (−14.6 to −6.1)
Satisfaction with pain relief after pain relief (316/198†*)	25.5	41.3	−15.7 (−20.2 to −11.2)
Pain during active labour (438/354)	29.7	24.9	4.9 (1.7 to 8.1)
Pain score after pain relief (345/220†)	27.8	21.0	7.0 (3.3 to 10.7)

*No who actually received pain relief.
†No who reported sufficient scores to calculate AUC and received pain relief.

Secondary outcomes

Overall scores and means

The overall satisfaction score with pain during labour was not significantly different between the study groups in the intention to treat analysis, when we accounted for scores of women with and without pain relief (6.9 remifentanil *v* 7.2 epidural, difference −0.29, 95% confidence interval −0.60 to 0.01). In women who received pain relief the overall satisfaction score was significantly lower for women randomised to remifentanil: 6.8 for women randomised to remifentanil *v* 7.3 for women randomised to epidural analgesia (difference −0.52, 95% confidence interval −0.91 to −0.13).

Mean scores for satisfaction with pain relief were significantly lower in the remifentanil group, both for the total period of active labour and after the start of pain relief. Mean pain scores for both periods were significantly higher in the remifentanil group. Pain scores and satisfaction with pain relief at the time when pain relief was requested were not significantly different between the groups. Highest satisfaction with pain relief and lowest pain intensity score after pain relief were significantly different in favour of epidural analgesia (table 4). These scores were not imputed.

Table 4. Secondary outcomes for mean (SD) pain scores and scores for satisfaction with pain relief in pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour. Missing values were not imputed.

	Remifentanil	Epidural analgesia	Difference (95% CI)	P value
Satisfaction with pain relief during active labour	5.1 (2.3)	5.9 (2.5)	–0.77 (–1.1 to –0.43)	<0.001
Satisfaction with pain relief after pain relief	5.3 (2.3)	7.0 (2.5)	–1.7 (–2.1 to –1.3)	<0.001
Satisfaction with pain relief at request pain relief	4.2	4.3	–0.12 (–0.58 to 0.35)	0.63
Highest satisfaction with pain relief after pain relief	6.9 (2.7)	8.4 (2.3)	–1.5 (–2.0 to –1.1)	<0.001
Pain during active labour	6.0 (1.9)	5.2 (2.3)	0.74 (0.46 to 1.0)	<0.001
Pain after pain relief	6.1 (1.9)	4.2 (2.3)	1.9 (1.5 to 2.3)	<0.001
Pain at request pain relief	7.7 (2.4)	7.7 (2.5)	0.03 (–0.32 to 0.38)	0.87
Lowest pain score after pain relief	4.0 (2.6)	1.7 (2.3)	2.3 (1.9 to 2.7)	<0.001

Characteristics of labour and maternal and neonatal outcomes

The intervals from request for pain relief to the start of pain relief and from start of pain relief to delivery were shorter in the remifentanil group (table 5). There were no other significant differences in characteristics of labour and maternal and neonatal outcomes between the two study groups (table 5).

In women who actually received analgesia, the only significant difference in characteristics of labour and maternal and neonatal outcomes was a shorter duration of second stage of labour in women randomised to remifentanil (0.42, 0.18 to 0.85 hour) compared with epidural analgesia (0.57, 0.25 to 1.00 hour) (P=0.01). Some side effects were reported more often in women who received analgesia. Temperature was significantly higher and hypotension more common in the women who received epidural analgesia. Oxygen saturation was significantly lower with remifentanil. There were four reported cases of respiratory depressions of <8 breaths a minute in the remifentanil group and none in the epidural group. Nausea was more common in the group randomised to remifentanil, but vomiting and itching were not (table 6).

Table 5. Characteristics of labour in pregnant women allocated to patient controlled remifentanil or epidural analgesia according to intention to treat analysis.
Figures are numbers (percentage) unless otherwise indicated

	Remifentanil (n=687)	Epidural analgesia (n=671)	Relative risk (95% CI)	P value
Median (IQR) gestational age at delivery (weeks)	39.7 (38.3-40.7)	39.7 (38.3-40.7)	—	0.37
Onset of labour:				
Spontaneous	282 (41)	281 (42)	0.98 (0.88 to 1.09)	0.76
Induced	405 (59)	390 (58)	1.02 (0.91 to 1.32)	0.76
Requested pain relief	447 (65)	347 (52)	1.32 (1.18 to 1.48)	<0.001
Median (IQR) dilatation (cm) at request	4 (3-5)	4 (3-5)	—	0.94
Fetal condition at start pain relief (cardiotocography) (n=794):				
Optimal	400 (90)	315 (91)	0.96 (0.80 to 1.17)	0.71
Not optimal	44 (10)	32 (9)	—	
Meconium stained amniotic fluid	76 (11)*	80 (12)†	0.95 (0.80 to 1.13)	0.57
Augmentation with oxytocin	394 (58)	391 (58)	0.97 (0.87 to 1.08)	0.61
>24 hours rupture of membranes	50 (7)	48 (7)	1.01 (0.83 to 1.24)	0.92
Median (IQR) time (min) from request to start analgesia	28 (15-45)	55 (32-80)	—	<0.001
Median (IQR) duration of analgesia (min)	236 (128-376)	309 (181-454)	—	<0.001
Median (IQR) duration second stage (min)	20 (10-46)	24 (10-53)	—	0.09
Mode of delivery:				
Spontaneous	518 (75)	501 (75)	1.01 (0.90 to 1.15)	0.75
Vaginal instrumental	63 (9)	70 (10)	0.93 (0.77 to 1.13)	0.45
Caesarean section	106 (15)	100 (15)	1.01 (0.88 to 1.17)	0.87
Postpartum haemorrhage (≥1000 mL)	52 (8)‡	66 (10)§	0.86 (0.69 to 1.06)	0.13
Apgar score <7 at 5 min neonate 1	9 (1)	15 (2)	0.74 (0.44 to 1.25)	0.20
Neonate 1 pHa <7.10	22 (5)¶	28 (6)**	0.86 (0.63 to 1.19)	0.34
Spinal headache	1 (0.1)††	4 (0.6)‡‡	0.24 (0.03 to 2.18)	0.21
Major maternal complication	2 (0.3)	6 (0.9)	0.33 (0.07 to 1.61)	0.17
Maternal admission	419 (61)	416 (62)	0.98 (0.88 to 1.09)	0.70
Median (IQR) length of admission (days)	1 (1-3)	1 (1-3)	—	0.24
Neonatal admission	390 (57)	385 (57)	0.99 (0.89 to 1.10)	0.82
Median (IQR) length of admission neonate 1 (days)	1 (1-3)	1 (1-3)	—	0.13
Median (IQR) length of admission neonate 2 (days)	3 (2-5.75)	4.5 (2.25-13.25)	—	0.42

*3.2% (21) missing. †4.2% (28) missing. ‡2% (14) missing. §2.8% (19) missing. ¶28.7% (197) missing. **28.8% (193) missing. ††5.3% (23/447) missing. ‡‡6.6% (22/347) missing.

Table 6 Maternal side effects during administration of analgesia in pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour. Figures are numbers (percentage) unless otherwise indicated.

	Remifentanil (n=447)	Epidural analgesia (n=347)	Relative risk (95% CI)	P value	No (%) with missing data	
					Remifentanil	Epidural
Temperature °C						
>38 °C	35 (9)	55 (18)	0.66 (0.50 to 0.86)	<0.001	41 (9.2)	35 (10.1)
Maximum reported:						
Median (IQR)	37.0 (36.6-37.4)	37.3 (36.7-37.8)	—	<0.001	41 (9.2)	35 (10.1)
Range	35.0-39.4	35.1-40.4	—	—	—	—
Saturation %:						
<95%	154 (37)	37 (12)	1.63 (1.46 to 1.82)	<0.001	32 (7.2)	45 (13.0)
<92%	71 (18)	14 (5)	1.52 (1.35 to 1.71)	<0.001	58 (13)	73 (21)
Minimum reported:						
Median (IQR)	95 (93-97)	97 (96-98)	—	<0.001	58 (13)	73 (21)
Range	50-100	76-100	—	—	—	—
Hypotension (<90 mm Hg systolic)	29 (7)	38 (12)	0.75 (0.57 to 1.00)	0.03	26 (5.8)	19 (5.5)
Respiratory depression	4 (1)	0 (0)	—	0.15	83 (18.6)	99 (28.5)
Nausea	62 (21)	25 (12)	1.27 (1.09 to 1.49)	0.01	150 (33.6)	138 (39.8)
Vomiting	55 (18)	28 (13)	1.16 (0.97 to 1.38)	0.12	145 (32.4)	134 (38.6)
Itching	17 (6)	20 (10)	0.77 (0.54 to 1.10)	0.1	156 (34.9)	144 (41.5)

One serious adverse event was recorded: one woman who received epidural analgesia presented with eclampsia on the fourth day after delivery. There were no maternal deaths. Postpartum admission, duration of admission, and reasons for admission for mothers and neonates were comparable in both groups (table 5).

There were three intrauterine fetal deaths after randomisation, all before the start of labour. These were two singletons at a gestational age 41-42 weeks and the second twin of monochorionic twins at 35+6 with suspicion of acute twin to twin transfusion syndrome. Three neonates died postpartum, two singletons and one twin, all from congenital defects that were diagnosed during pregnancy (Zellweger syndrome, two major cardiac defects).

Subgroup analyses for AUC for pain and satisfaction with pain relief were performed as planned for all predescribed groups except for gestational age at birth 32-34 weeks because only one woman in the remifentanil group received pain relief. Results of subgroup analysis were similar to those of the whole group, with no significant interactions found (see figs A-D in appendix 3).

Discussion

Statement of principal findings

The results of this large multicentre trial show that patient controlled analgesia with remifentanil is not equivalent to epidural analgesia with respect to satisfaction with pain relief, with poorer scores obtained in women treated with remifentanil. This study also confirms the results of previous trials that epidural analgesia provides superior pain relief when measured in terms of pain intensity scores.[5,6,18-20] These results were consistent throughout all subgroups. In contrast with previous studies that did not have sufficient power to detect a difference, this is the first well powered study to showing that patient controlled remifentanil is not equivalent to epidural analgesia with respect to satisfaction with pain relief.

Significantly more women randomised to remifentanil actually requested and received analgesia. We relate this to the perception of women that remifentanil is less invasive and more easily available. Furthermore, the time between the request for and start of analgesia was shorter in the remifentanil group, probably because an anaesthetist is not required.

Duration of analgesia (that is, the time from start of analgesia to birth) was significantly longer in the epidural analgesia group. One explanation might be the epidural analgesia slows labour but there are other possible explanations. For example, in the Netherlands it is still practice to wait for the urge to push (and even to stop the epidural to increase sensation). This might cause a delay in starting the second stage of labour.

An important finding from the secondary outcome measures is the high incidence of desaturations, with oxygen saturations below 92% in 18% and below 95% in 38% of women treated with remifentanil, compared with 5% and 12% in women treated with epidural analgesia (table 6).

There were four reported respiratory depressions with <8 breaths a minute in the remifentanil group, all during administration of remifentanil. Although the difference in occurrence is not significant, probably because of the low prevalence of respiratory depression, and although there were about 25% missing values, this is a potentially life threatening side effect of remifentanil. Caregivers should be aware that serious respiratory complications can occur during administration of remifentanil (table 6).[19-22]

Strengths and weaknesses

In the Netherlands there is a distinction between primary and secondary/tertiary care in obstetrics. Women at low risk are under antenatal care of community midwives; intermediate or high risk women are under antenatal care of gynaecologists. We included only women in secondary/tertiary care as we assumed that opinions on labour and pain (satisfaction) are different not only in the women but also in the obstetric team. As we were interested in this possible difference, we started a second study in low risk women in primary care. This study has been completed and is under analysis.

We decided to use the area under the curve (AUC) as our primary outcome as it included all available data from responders and can be interpreted as an integral measure of total satisfaction

with pain relief rather than using satisfaction only at a specific time point. The AUC gives a time weighted measure of total satisfaction with pain relief.

We measured satisfaction scores at one hour intervals during active labour and used the AUC as a time weighted measure of this index. Use of AUC requires multiple scores during labour. This could have resulted in an increase in missing data as in some women, especially those women who did not receive pain relief, often just one measurement was available. Still we chose this approach as pain AUC gives a time weighted and consequently a more reliable measure of pain response than single measurements.

Though we believe that a time weighted measure is the best way to measure total satisfaction with pain relief, pain relief was administered over a longer period of time in the epidural analgesia group. This influences the AUC but it also influences total pain experience (with a higher total satisfaction over a longer period of time). To test if the difference in AUC between the two study groups during administration of pain relief was influenced by this difference we also analysed the AUC per hour and mean satisfaction with pain relief on specific time points. As these were also significantly lower in the remifentanil group, we believe the total AUC is only minimally influenced by this extra time.

The main weakness of our study was the percentage of missing values for satisfaction with pain relief and pain intensity. The AUC for satisfaction with pain relief during active labour could be calculated for 57% of women in the remifentanil group and 43% in the epidural group. In the subgroup of women who actually received analgesia, the AUC for satisfaction with pain relief during administration of pain relief could be calculated for 71% and 57%, respectively.

As mentioned above, multiple measurements are necessary to calculate the AUC. One explanation for the missing data is reluctance of caregivers to focus on pain in women who are not asking for pain relief. Another reason might be that epidural analgesia is routine so extra measurements are more easily forgotten. We opted to use imputation to correct for these missing values, assuming that scores for satisfaction with pain relief were missing at random. Hence, we judged that imputation would give a more accurate representation of total satisfaction with pain relief than the exclusion of women with just one or no data points.[15] The groups with complete and incomplete data were similar on all baseline characteristics and most labour characteristics. They were, however, significantly different on onset of labour, request for pain relief, and mode of delivery, with fewer scores obtained from women in spontaneous labour who did not receive pain relief and delivered spontaneously. This could be explained by shorter duration of labour and shorter time in hospital for those women. Furthermore, analyses without imputed values showed similar differences in AUC for pain intensity and satisfaction with pain relief.

As randomisation was performed antenatally, women knew their allocated intervention when in need for pain relief during labour. We chose this design to mimic daily practice, where a woman knows which methods of pain relief are available and which one she will most likely receive. Because masking of treatment was considered unethical, crossovers might have occurred because of preferences of doctors or women for one of the two treatments in light of labour characteristics. This could have influenced study outcome to some extent. But as the percentage of non-compliance in both groups was around 10%, lower than the number we anticipated in the power analysis, we think

this influence was minimal. Furthermore, in an equivalence design non-compliance will provide an underestimation of the effect, making it more plausible that there truly is no equivalence between both interventions.

Explanation and implication for clinicians and policymakers

Although patient controlled remifentanil does improve pain and scores for satisfaction with pain relief, our study shows that this improvement is not optimal when compared with improvement of scores with epidural analgesia. As scores for satisfaction with pain relief were lower and pain intensity scores higher in women randomised to remifentanil, we cannot suggest it as an equivalent alternative to epidural analgesia. The higher percentage of women who actually received pain relief in the remifentanil group could suggest that there is a need for other types of analgesia options besides epidural analgesia and that women and/or caregivers perceive remifentanil as less invasive and hence easier to administer and possibly also less harmful. Another explanation might be that remifentanil is more readily available than epidural analgesia because the presence of an anaesthetist is not required. Either patient controlled remifentanil is a much needed addition to the possibilities of analgesia or we should still make epidural analgesia more accessible for all women who request pain relief during labour.

Delivery outcome and labour characteristics were not different between groups nor were maternal and neonatal morbidity. But we did find a significant difference in respiratory side effects in women treated with remifentanil. Remifentanil is a potent opioid and should be used with appropriate monitoring and the ability to intervene if respiratory complications arise.[20,21] Women should be counselled on the effects and side effects of both remifentanil and epidural analgesia.

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Appendix

Table 1. Baseline characteristics complete and incomplete cases, AUC during active labour

	AUC no (incomplete)	AUC yes (complete)	p value
Gestational age at randomisation (weeks; median [IQR])	37.9 [36.2-39.4]	37.9 [35.8-39.4]	0.66
Maternal age (years; means [SD])	31.5 [5.1]	31.5 [5.4]	0.96
Ethnic origin*			
Caucasian	240 (91%)	450 (85%)	0.05
Education			
≥HBO	289 (50%)	288 (50%)	0.13
Body mass index (median [IQR])	24.2 [21.8-27.5]	24.2 [21.7-27.8]	0.28
ASA classification			
ASA 1	185 (70%)	374 (71%)	0.80
ASA 2	80 (30%)	155 (29%)	
Parity			
0	144 (54%)	294 (56%)	0.74
≥1	121 (46%)	235 (44%)	
Multiple pregnancy	16 (5.9%)	20 (3.7%)	0.26

Table 2. Labour characteristics complete and incomplete cases, AUC during active labour

	AUC no (incomplete)	AUC yes (complete)	p value
Gestational age at delivery (days; median [IQR])	278 [267-285]	278 [269-285]	0.07
Onset of labor			
Spontaneous	344 (49%)	219 (33%)	<0.001
Induced	354 (51%)	441 (67%)	
Request pain relief			
Yes	265 (38%)	529 (80%)	<0.001
Dilatation at request pain relief (cm; median [IQR])	4 [3-5]	4 [3-5]	0.28
Fetal condition at start pain relief (CTG) n=794			
Optimal	389 (90%)	539 (91%)	0.61
Not optimal	41 (10%)	52 (9)	
Meconium stained amniotic fluid	73 (11%)	83 (13%)	0.20
Augmentation with oxytocin	343 (49%)	453 (69%)	<0.001
>24 hours ROM	47 (7%)	51 (8%)	0.48
Time from request to start analgesia (hours, median [IQR])	0.69 [0.42-1.2]	0.57 [0.28-1.0]	0.49
Duration of analgesia (hours, median [IQR])	4.4 [2.2-7.1]	4.6 [2.5-7.1]	0.58
Duration second stage of labour (hours, median [IQR])	0.30 [0.15-0.77]	0.43 [0.17-0.90]	0.01
Mode of delivery			
Spontaneous	557 (80%)	462 (70%)	<0.001
Vaginal instrumental	50 (7%)	83 (13%)	
Caeserean section	91 (13%)	115 (17%)	
Postpartum haemorrhage (≥1000 ml)	59 (9%)	59 (9%)	0.79
Apgar score <7 neonate 1			
5 min	12 (2%)	12 (2%)	0.89
pHa <7.10 neonate 1	28 (6%)	22 (5%)	0.46

Table 1. Baseline characteristics complete and incomplete cases, AUC after pain relief

	AUC no (incomplete)	AUC yes (complete)	p value
Gestational age at randomisation (weeks; median [IQR])	37.9 [36.2-39.4]	37.9 [35.8-39.4]	0.99
Maternal age (years; means [SD])	31.4 [5.1]	31.5 [5.4]	0.87
Ethnic origin*			
Caucasian	272 (90%)	418 (86%)	0.11
Education			
≥HBO	133 (46%)	221 (54%)	0.96
Body mass index (median [IQR])	24.2 [21.8-27.5]	24.2 [21.7-27.8]	0.26
ASA classification			
ASA 1	205 (68%)	354 (72%)	0.18
ASA 2	98 (32%)	137 (28%)	
Parity			
0	165 (54%)	273 (56%)	0.75
≥1	138 (46%)	218 (44%)	
Multiple pregnancy	15 (4.9%)	16 (3.3%)	0.29

Table 2. Labour characteristics complete and incomplete cases, AUC after pain relief

	AUC no (incomplete)	AUC yes (complete)	p value
Gestational age at delivery (days; median [IQR])	278 [268-287]	278 [270-286]	
Onset of labor			0.93
Spontaneous	104 (34%)	167 (34%)	
Induced	199 (66%)	324 (66%)	
Dilatation at request pain relief (cm; median [IQR])	4.0 [3.0-5.0]	3.9 [3.0-5.0]	0.35
Fetal condition at start pain relief (CTG) n=794			
Optimal	272 (90.7%)	443 (90.2%)	0.84
Not optimal	28 (9.3%)	48 (9.8%)	
Meconium stained amniotic fluid	30 (11%)	62 (14%)	0.25
Augmentation with oxytocin	199 (66%)	340 (69%)	0.31
>24 hours ROM	20 (7%)	41 (8%)	0.37
Time from request to start analgesia (hours, median [IQR])	0.70 [0.42-1.2]	0.76 [0.27-1.0]	0.15
Duration of analgesia (hours, median [IQR])	4.2 [2.1-7.2]	4.7 [2.6-7.0]	0.23
Duration second stage of labour (hours, median [IQR])	0.45 [0.22-1.0]	0.47 [0.20-0.88]	0.55
Mode of delivery			
Spontaneous	192 (72%)	355 (67%)	0.27
Vaginal instrumental	28 (11%)	73 (14%)	
Caeserean section	45 (17%)	101 (19%)	
Postpartum haemorrhage (≥1000 ml)	28 [9.3%	42 [8.7%]	0.77
Apgar score <7 neonate 1			0.72
5 min	8 (2.7%)	11 (2.3%)	
pHa <7.10 neonate 1	17 (7.4%)	20 (5.4%)	0.32

5

An economic analysis of patient controlled remifentanil and epidural analgesia as pain relief in labour (RAVEL trial); a randomised controlled trial

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Submitted

Abstract

Objective: To compare the costs of a strategy of patient controlled remifentanil versus epidural analgesia for pain relief in labour.

Design: We performed a multicentre randomised controlled trial in 15 hospitals in the Netherlands, the RAVEL trial. Costs were analysed from a health care perspective alongside the RAVEL trial.

Population: Pregnant women of intermediate to high risk beyond 32 weeks gestation who planned vaginal delivery.

Methods: Women were randomised before the onset of labour, to receive either patient controlled remifentanil or epidural analgesia when pain relief was requested during labour.

Main outcome measures: Primary outcome for effectiveness was satisfaction with pain relief, expressed as the area under the curve (AUC). A higher AUC represents higher satisfaction with pain relief. Here, we present an economic analysis from a health care perspective including costs from the start of labour to ten days postpartum. Health-care utilization was documented in the Case Report Forms and by administering an additional questionnaire.

Results: The costs in the patient controlled remifentanil group (n=687) and in the epidural group (n=671) were €2900 versus €3185 respectively (mean difference of -€282 (95% CI -€611 to €47)). The (non-significant) higher costs in the epidural analgesia group could be mainly attributed to higher costs of neonatal admission.

Conclusion: From an economic perspective, there is no preferential pain treatment in labouring intermediate to high risk women. Since patient controlled remifentanil is not equivalent to epidural analgesia with respect to AUC for satisfaction with pain relief we recommend epidural analgesia as the method of choice. However, if appropriately counselled on effect and side effects there is, from an economic perspective, no reason to deny women patient controlled remifentanil.

Introduction

Epidural analgesia is considered to be the most effective analgesia during labour.[1] In recent years patient controlled remifentanil was introduced as pain relief during labour. Remifentanil is an opioid which is very suitable for administration through patient controlled analgesia (PCA).[2] Remifentanil crosses the placenta but is rapidly metabolised by the fetus.[3]

Previous studies on patient controlled remifentanil versus epidural analgesia report superior analgesia with epidural analgesia but comparable patient satisfaction.[4,5] However, these studies were small and potentially underpowered in their assessment of equivalence. We recently performed a large randomised equivalence trial to compare effects and costs of patient controlled remifentanil to epidural analgesia (RAVEL trial NTR 2551). The effectiveness study shows that women randomised to epidural analgesia were significantly more satisfied with analgesia than women randomised to remifentanil PCA with no differences in labour characteristics, neonatal parameters (Apgar score and umbilical cord pH) and maternal and neonatal admission. More women in the remifentanil group received analgesia (RR 1.3, 95% CI 1.2 to 1.5). Respiratory side effects were reported more frequently in the remifentanil group and maternal temperature was higher in the epidural group.[6,7]

Only one study has been published on costs of epidural analgesia versus intravenous opioids.[8] Incremental costs for women treated with epidural analgesia were calculated based on literature review on complications and additional costs of involvement of an anaesthetist. Incremental costs were found to be $338, largely because of the increase in costs due to involvement of an anaesthesiologist.

This study reports the cost evaluation based on primary data that was performed alongside the RAVEL trial. We expected costs to be lower in the group randomised to patient controlled remifentanil as the involvement of an anaesthetist is not required.

Material and methods

The economic analysis was performed alongside the RAVEL trial, which full design has been reported previously.[6,7] The trial was approved by the Central Committee on Research Involving Human Subjects and the Medical Ethics Committee of the Leiden University Hospital (p10-240) and the Boards of Directors of the participating centres. The trial has been registered in the clinical trial register as NTR-2551.

In short, the RAVEL trial was a randomised controlled equivalence trial conducted from May 30th 2011 until October 24th 2012 in 15 centres in the Netherlands. Healthy women (American Society of Anesthesiologists' class 1 or 2 [9]), >17 years with an intermediate to high obstetric risk who planned to deliver vaginally after 32 weeks were eligible to participate. They were randomly allocated to receive patient controlled remifentanil or epidural analgesia should they request pain relief during labour. After being informed of the study by their primary caregiver, written informed consent of the woman, was obtained at antenatal visits before onset of actual labour. There was no separate informed consent obtained for neonatal information.

Women randomised to receive remifentanil were on their request treated with remifentanil through a PCA (patient controlled analgesia) device. Women randomised to epidural analgesia were treated on their request with epidural analgesia according to local protocol.

1414 women were randomised of whom 51 women were excluded after randomisation because they delivered through elective caesarean section. There were three women lost to follow up and two women withdrew consent after randomisation; all in the epidural group. The median of the number of randomised women per hospital was 64 with an interquartile range (IQR) of 24-164. The flowchart and baseline characteristics of these women are reported elsewhere.[7] Data of all randomised women, 687 to patient controlled remifentanil and 671 to epidural analgesia were used in the costs analysis.
Economic analysis was performed from a health care perspective with a time horizon from the start of active labour until 10 days after delivery. Costs were converted to 2014 euros using the consumer price index.[10]

Our published protocol stated that both effectiveness and cost-effectiveness were primary outcome measures. Satisfaction with pain relief was the primary outcome measure for effectiveness from the start of the study. As planned we performed a cost effectiveness analysis as well, taking into account the primary outcome for effectiveness. Because this was not made clear enough in the original protocol and registry it was changed in the last amended protocol. This last amended protocol was submitted before delivery of the last randomised woman and as a result we did not have access to the data.[7]

Resource use

Health-care utilisation was documented in the Case Report Form and by administering an additional questionnaire. Items listed in the Case Report Form were use of medication during labour, medication used in epidural analgesia and the duration of analgesia, involvement of the anaesthetist in administration of remifentanil, type of delivery (spontaneous, operative vaginal or caesarean section), repair of perineal tear in theatre, manual removal of placenta, medication used to treat postpartum haemorrhage, blood transfusion, maternal and neonatal admission (type and duration). Use of health care after discharge from the hospital was reported by participating women and measured using an additional questionnaire. Contact with general practitioner, midwife, obstetrician, paediatrician and emergency department were recorded.

Unit costs

For mode of delivery, operative interventions in the third stage and maternal and neonatal admission unit costs were collected from two university and two teaching hospitals. Obtained unit costs were used to calculate mean unit costs. Unit cost of maternal admission was divided into maternal ward, medium care or intensive care, for each admission. Neonatal admission was also differentiated into different levels of care, neonatal admission at the ward, medium care or high/intensive care.

For other unit costs, outpatient visit, visits to general practitioner, emergency department, and blood transfusion Dutch standardised prices were used[11] which were converted to 2014 euros.[10] Medication prices were obtained from the website of the pharmacotherapeutic compass.[12] Unit costs of postpartum care by community midwives were calculated using standards for yearly labour- and practice costs of midwives of the Dutch Healthcare Authority and converted to costs per hour with estimates of the yearly number of working hours of midwives of the Dutch Society for Midwifery (KNOV).

To calculate the costs of analgesia we used a bottom up approach. These costs consist of the epidural catheter and the equipment used to insert the catheter, the costs of medication used and personnel costs. Costs of the material used to insert the epidural catheter and administer medication were obtained from the purchasing department of one hospital. For personnel costs we used expert opinion of anaesthetists in two hospitals (one university and one teaching) on duration of care. For epidural analgesia this was estimated to be 30 minutes for nursing staff and 30 minutes for the anaesthetist. For patient controlled remifentanil it was advised in the study protocol to have one to one nursing for the first hour after starting analgesia. For centres where the anaesthetist was present at the start of patient controlled remifentanil their presence on the labour ward was estimated to be 20 minutes.
The amount of remifentanil used was calculated as was the amount of medication (opioids and/or local anaesthetic) used in epidural analgesia per woman based on duration of administration of analgesia. Next to equipment, material, personnel and medication costs an increment of 42%[11] of the direct costs was included for housing, depreciation and overhead. (Table 1)

Table 1. Cost-analyses: units of resource use, unit costs, valuation method and volume source (2014 €)

		Unit	Unit cost	Valuation method (source)	Volume source
Direct health care costs					
Admission costs					
	Admission mother				
	hospital stay - ward	day	377	real costs (2)	CRF
	hospital stay - medium care	day	605	real costs (2)	CRF
	hospital stay - intensive care	day	1955	real costs (2)	CRF
	Admission child				
	hospital stay - ward	day	377	real costs (2)	CRF
	hospital stay - medium care	day	605	real costs (2)	CRF
	hospital stay - neonatal intensive care	day	1640	real costs (2)	CRF
	Ambulance transport	ride	292	guideline (1)	CRF
Personnel costs	Specialist care after discharge				
	Outpatient visit mother/neonate	visit	80	guideline (1)	AQ
	Emergency department	visit	168	guideline (1)	AQ
	General practicioner	house visit	48	guideline (1)	AQ
		visit	31	guideline (1)	AQ
		telephone contact	16	guideline (1)	AQ
	Midwife	hour	86	KNOV(3)	AQ
Delivery	*Medication during labour*				
	Oral antihypertensiva	costs per day	0.39	real costs (4)	CRF
	Oxytocin	total costs labour	0.59	real costs (4)	CRF
	Antibiotics	total costs labour	7	real costs (4)	CRF
	Fetal blood sampling	total costs labour	17	STAN trial (7)	CRF
Pain relief during labour	Patient controlled remifentanil	procedure	10	real costs (6)	CRF
	Epidural analgesia	procedure	19	real costs (6)	CRF
	Anaesthetist	hour	115	guideline (1)	CRF
	Nurse	hour	31	guideline (1)	CRF
	Equipment administration and monitoring remifentanil	procedure	6	real costs (6)	
	Equipment administration and monitoring epidural	procedure	15	real costs (6)	
Mode of delivery	Spontaneously	procedure	886	real costs (2)	CRF
	Ventouse delivery	procedure	973	real costs (2)	CRF
	Forcipal extraction	procedure	973	real costs (2)	CRF
	Caesarean section	procedure	1258	real costs (2)	CRF

Third stage	Blood transfusion				
	Red blood cells	product	224	guideline (1)	CRF
	Fresh frozen plasma	product	193	guideline (1)	CRF
	Platelets	product	541	guideline (1)	CRF
	Medication third stage				
	Oxytocin	dose per day	1	Pharmacotherapeutic website (4)	CRF
	Sulprostone	dose per day	149	Pharmacotherapeutic website (4)	CRF
	Balloon (Cook/Bakri)	product	176	real costs (5)	CRF
Interventions post partum	Repair perineal tear in operating theatre	procedure	1057	real costs (2)	CRF
	Manual removal placenta	procedure	711	real costs (2)	CRF
	Incomplete placenta, manual removal	procedure	682	real costs (2)	CRF
	Laparotomie	procedure	1518	real costs (2)	CRF

CRF case record form
AQ additional questionnaire

Source:
1 Hakkaart, 2010
2 Unit cost calculation (top-down) of 2 general and 2 academic hospitals
3 KNOV (Royal Dutch Organisation of Midwives)
4 www.medicijnkosten.nl
5 Purchasing department LUMC
6 bottom-up cost calculation
7 Vijgen S et al. Cost-effectiveness of cardiotocography plus ST analysis of the fetal electrocardiogram compared with cardiotocography only. Acta Obstet Gynecol Scand. 2011 Jul;90(7):772-8.

Analyses

Resource use per woman was multiplied by unit costs and total costs per woman were calculated. Mean costs differences between groups were tested using the Student's t-test. Use of analgesia was compared using the Chi-square test. We used multiple imputation with SPSS to correct for missing primary outcome data.[13-15] We imputed missing AUC values for satisfaction with pain relief and pain intensity (transformed so that the distribution was approximately normal) using 20 imputed datasets. Missing values that were imputed for the cost analysis were use of oxytocin, pain relief and admission mother (all missing < 1%), admission child (missing 2%), costs of fetal scalp sampling (missing 21%), use of antibiotics during labour (missing 39%), and costs of health care after discharge (missing 56%).

Additionally we added scenario analysis post hoc to address the influence of the presence of an anaesthetist at the start of patient controlled remifentanil and to address the influence of continuous one to one nursing during administration of remifentanil. We did not plan these analysis beforehand but after the trial ended and before analysis the Dutch Heath Care Inspectorate (IGZ) initiated the development of a Standard Operating Procedure (SOP) for the administration of patient controlled remifentanil on the labour ward.[16] One of the recommendations is continuous one to one care for

women treated with remifentanil. As this could influence costs we decided to perform the scenario analyses. Statistical and economic analyses were performed using SPSS version 20 (SPSS, Chicago, IL).

Results

Use of analgesia

In the patient controlled remifentanil group 448 women (65%) received analgesia versus 347 women (52%) in the epidural analgesia group (RR 1.3 95% CI 1.2-1.5). Of the 448 women in the remifentanil group receiving pain relief, 403 women received immediate remifentanil, of these 53 converted to epidural analgesia, 41 women received epidural analgesia and four received other opioids. Of the 347 women requesting pain relief allocated to epidural analgesia, 298 received immediate epidural analgesia (3 were also treated with patient controlled remifentanil because of insufficient pain relief), 32 were treated with patient controlled remifentanil (of whom 2 women converted to epidural analgesia after remifentanil) and 17 with other opioids.

Costs

Costs per patient are presented in table 2. Mean costs for women randomised to patient controlled remifentanil were €2900 versus €3183 for women randomised to epidural analgesia (mean difference -€282 (95% CI -€611 to €47)). The largest part of this difference can be attributed to the higher costs of neonatal admission in the epidural group. This non-significant difference in costs for neonatal admission was -196 (95%CI -465 to 73).

Breaking down the costs of analgesia costs for medication are higher in the remifentanil allocated group whereas costs for equipment and material are higher in the epidural allocated group (table 2).

Scenario analysis

Scenario analysis of the presence of an anaesthetist at the start of patient controlled remifentanil and continuous one to one care are presented in table 3 and 4. Taking only the costs of analgesia into account, the costs of patient controlled remifentanil increase when an anaesthetist is present at the start of analgesia and increase even more with continuous one to one nursing. Only when no anaesthetist is involved in the administration of patient controlled remifentanil and there is one to one nursing for only the first hour there is a significant difference in costs of analgesia in favour of patient controlled remifentanil. In all other scenarios costs of epidural analgesia are significantly lower, resulting in even more comparable total costs between both groups.

Table 2. Costs per woman (2014 €).

	Patient controlled remifentanil		Epidural analgesia		mean difference	95% CI	p value
	mean costs pp	% patients using care	mean costs pp	% patients using care			
Analgesia							
equipment and material	6		15		-9	-10.3 to -7.3	<0.001
personnel	34		35		-0.4	-4.2 to 3.4	8.4
medication	13		5		7.7	6.4 to 9.0	<0.001
overhead*	22		23		0.6	-3.2 to 1.9	0.63
Total analgesia	**76**	**65**	**78**	**49**	**-2**	-10.8 to 6.6	0.64
Delivery	953	100	957	100	-5	-22 to 12	0.56
Medication during labour							
antihypertensives	0.03	9	0.03	8	0	-0.01 to 0.02	0.52
oxytocin	0.37	62	0.37	49	0	-0.04 to 0.02	0.59
antibiotics	0.35	4	0.48	9	-0.13	-0.53 to 0.27	0.53
Fetal scalp sampling	14	24	14	24	-0.17	-5.1 to 4.8	0.94
Medication third stage	7	12	7	14	-0.62	-6.8 to 5.5	0.84
Operative removal (incomplete) placenta	32	5	39	6	-7	-23 to 10	0.41
Repair of perineal tear in theatre	60	6	60	6	0.14	-25 to 26	0.99
Blood transfusion	11	2	19	3	-8	-19 to 3.1	0.16
Total delivery	**1154**		**1175**				
Maternal admission	560	62	619	63	-59	-132 to 14	0.11
Neonatal admission	1027	60	1223	63	-196	-465 to 73	0.15
10 days postpartum							
Midwife	99	96	101	96	-1	-7.7 to 5.5	0.74
General practicioner	30	48	29	48	2	-5.6 to 8.7	0.67
Obstetrician	11	5	10	6	-0.62	-8.2 to 9.4	0.89
Pediatrician	14	11	17	12	-4	-10 to 2.8	0.26
Emergency department	8	4	9	6	-2	-7.3 to 4.2	0.59
Total postpartum	**162**		**166**				
Total	**2900**		**3183**		**-282**	-611 to 47	0.09

*42% of direct costs (Hakkaart et al. 2010)

Table 3. Scenario analyses. Total costs.

	Remifentanil PCA	Epidural analgesia	difference	95% CI	p value
RAVEL trial	76	78	-2.1	-11 to 7	0.63
Scenario 1	67	77	-10	-18 to -2	0.02
Scenario 2	99	80	19	10 to 28	<0.001
Scenario 3	126	80	46	33 to 58	<0.001
Scenario 4	158	83	75	61 to 89	<0.001

Table 4. Scenario analyses. Costs of analgesia.

	Remifentanil PCA	Epidural analgesia	difference	95% CI	p value
RAVEL trial	2900	3183	-282	-611 to 47	0.09
Scenario 1	2892	3182	-290	-619 to 38	0.08
Scenario 2	2924	3185	-261	-590 to 68	0.12
Scenario 3	2951	3186	-235	-564 to 95	0.16
Scenario 4	2983	3189	-205	-535 to 124	0.22

Scenario 1: the anesthetist is never involved in starting patient controlled remifentanil. One to one nursing 1 hour.
Scenario 2: the anesthetist is always involved in starting patient controlled remifentanil. One to one nursing 1 hour.
Scenario 3: the anesthetist is never involved in starting patient controlled remifentanil. One to one nursing for the whole duration of administration of pain relief.
Scenario 3: the anesthetist is always involved in starting patient controlled remifentanil. One to one nursing for the whole duration of administration of pain relief.

Discussion

Main findings

To our knowledge this is the first study comparing the costs of patient controlled remifentanil and epidural analgesia during labour. We assessed the costs of a strategy of patient controlled remifentanil compared to epidural analgesia. Costs were analysed from a health care perspective alongside the RAVEL trial. Mean costs did not differ significantly between the two groups (mean difference -€282 (95% CI -€611 to €47), the largest difference was noted in the costs for neonatal admission. Scenario analyses show that costs of analgesia change when the anaesthetist is present and with continuous one to one nursing with patient controlled remifentanil, increasing the costs of pain relief in the remifentanil allocated group and thus increasing total costs resulting in a smaller difference between groups.

Interpretation

We hypothesised that satisfaction with analgesia of women using patient controlled remifentanil would be equivalent to epidural analgesia. If this would be the case, women could have access to adequate analgesia with the possibility of lower costs because the presence of an anaesthetist is not required for the administration of remifentanil. Because of the low costs of both types of

analgesia compared to the total costs of delivery and the post-partum period we did not show a significant difference in costs in both groups. Furthermore, the advice to provide one to one nursing of women on remifentanil in the SOP attached to the Dutch guideline will result in higher costs for remifentanil than estimated in this study, resulting in even more comparable total costs. However, latest evidence shows that one to one nursing is beneficial for all women in labour, independent of receiving analgesia or not.[17] Since this will increase costs in both groups, as shown in table 4 scenario 3 and 4, the total difference will stay the same with a non-significant difference in costs between groups.

Costs for neonatal admission in the group randomised to epidural analgesia are almost 200 euro higher per woman, but this was not statistically significant. A possible explanation could be that mean duration of neonatal admission is 25% longer, although not statistically different, in the epidural group (mean 1.9 versus 2.5 days; p=0.11). Also, as there are no differences in Apgar score, umbilical cord pH or reasons for admission we did not find an explanation for these higher costs. Reasons for admission did not differ between groups.

Strengths and limitations

Strength of this study is the fact that it is a large randomised controlled trial with prospective collection of data and resource use which was performed in 15 centres within the well-organised structure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. The study also has several limitations, the first being the percentage of missing data.

The reporting of missing data in trial-based economic evaluations and the methods used to handle missing data are varied and unclear. There are several ways to deal with missing data, the use of multiple imputation is valid when data are judged to be missing at random. We used multiple imputation for the primary outcome measure (satisfaction with pain relief) as well as for several economic variables because of missing values. Most missing variables were missing in less than 5%, only 3 were missing more than 5%. The variable with the most missing values was postpartum care after discharge. This variable was evaluated with an additional questionnaire, of which the response rate was 43.7%. Because there were no big differences between women in care postpartum reported in the questionnaires, and care postpartum in the Netherlands is standardised with three or four home visits by a community midwife and often one visit by a general practitioner, we judged that imputation would give a representative result.

Furthermore, we did not specifically ask for readmission (not in the CRF nor in the questionnaire) so we could not evaluate costs due to readmission for complications. This could potentially influence results when one group would be more prone to developing complications which would lead to admission (infection for example). However, complications were recorded in the CRF and not significantly different in both groups.

Women were randomised before start of labour and informed about the result of randomisation. While this could be a potential source of bias for our analysis for effectiveness (as was previously published)[6] this is actually a strength for economic evaluation. To be suitable for economic evaluation a trial should be pragmatic and ideally set up for measuring effectiveness (i.e. test an

intervention under real life conditions).[18] Knowing which analgesia is available when there is a need can influence if analgesia is requested, thus influencing costs. There were significantly more women, randomised to remifentanil, who actually requested and received analgesia. We relate this to the perception of women that remifentanil is less invasive and more easily available.

After careful consideration we decided not to perform a cost-effectiveness analysis since we deemed it impossible to decide what a loss of 1 point in the AUC of satisfaction with pain relief is worth in costs. So performing this cost-effectiveness analysis would not have any clinical meaning.

We stated that our multi-centre design is a strength of this study however, inter-site differences could invoke additional variability making our strength a limitation. We repeated our costs analysis using mixed-effect modelling. This resulted in marginal differences: total costs in this analysis is €-258 95% CI [-63 to 580] p=0.12 and in our original analysis € -282 [-47 to 611] p=0.09.[6]

Conclusion

From an economic perspective, there is no preferential pain treatment in intermediate to high risk labouring women. Since patient controlled remifentanil is not equivalent to epidural analgesia with respect to AUC for satisfaction with pain relief in labouring women we recommend epidural analgesia to be the treatment of choice. However, if appropriately counselled on effect and side effects there is, from an economic perspective, no reason to deny women patient controlled remifentanil.

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6

Maternal temperature and oxygen saturation in women using remifentanil patient controlled analgesia and epidural analgesia for pain relief during labour; a sub analysis of the RAVEL trial

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Submitted

Abstract

Background: Epidural analgesia and remifentanil patient controlled analgesia are two popular techniques for the treatment of labour pain, each with its own efficacy and side-effects.

Methods: We performed a multicentre randomised controlled clinical trial, the RAVEL trial. Women who intended to deliver vaginally were randomised before the onset of active labour to receive remifentanil patient controlled analgesia or epidural analgesia. Main outcome measures for this sub-analysis were maternal peripheral oxygen saturation and temperature recorded hourly. Data are presented as means and analysed using repeated measurement analysis to account for the correlated observations within persons.

Results: We analysed the results of women receiving analgesia, 444/709 women in the remifentanil group and 329/705 women in the epidural analgesia group. Baseline characteristics were comparable between groups except for parity with less parous women receiving epidural analgesia. Mean oxygen saturation was significantly lower in the remifentanil group with a significant higher percentage of women experiencing low SpO2 (<92%). Type of analgesia did influence maternal peripheral oxygen saturation, with the remifentanil group having a significantly lower peripheral saturation (p=<0.001). Mean temperature was significantly higher in the epidural analgesia group as was the incidence of fever (T >38°C). Type of analgesia influenced maternal temperature, with a higher maternal temperature in the epidural analgesia group (p<0.001).

Conclusion: Maternal temperature and incidence of fever are higher in parturients using epidural analgesia. Desaturation is more frequent in women randomised to remifentanil and not limited to a certain period after the start of analgesia.

Introduction

Epidural analgesia is considered the most effective form of analgesia during labour because of the most efficient reduction of pain intensity scores.[1] However, epidural analgesia can be contra-indicated in women with coagulopathy or musculoskeletal disorders. A known side-effect of epidural analgesia is an increase in maternal temperature.[1-5] The consequence of maternal fever during labour can be admission of the neonate to the neonatal ward and administration of antibiotics for suspicion of sepsis. The suggested mechanism for the increase in maternal temperature is an alteration of thermoregulation.[2] Remifentanil patient controlled analgesia seemed a promising alternative for women who cannot or do not wish to receive epidural analgesia. Remifentanil is a potent μ-opioid receptor agonist with an onset to effect of 30-60 seconds and time to peak effect of 2.5 min.[6] Because of these characteristics remifentanil is suitable for administration through patient controlled analgesia (PCA). Although it crosses the placenta it is rapidly metabolised and distributed by the fetus.[7]

There has been a rapid increase in the use of remifentanil patient controlled analgesia as method of analgesia during labour in the past decade. However, studies showed that remifentanil is inferior to epidural analgesia with respect to efficacy (i.e. decrease in pain intensity score)[8,9] and satisfaction with pain relief.[10]

The most important known side-effects of remifentanil are respiratory complications. Oxygen saturation in women on remifentanil patient controlled analgesia was significantly lower[10,11] and episodes of SpO2 < 92% and < 90% were more frequent and lasted longer with remifentanil patient controlled analgesia compared to epidural analgesia or no analgesia.[5] Furthermore, Stocki et al. described apnoea in 5/19 women during the first hour of using remifentanil patient controlled analgesia, with SpO2 >92% in most cases.[11]

The RAVEL trial (remifentanil patient controlled analgesia versus epidural analgesia in labour) was performed to assess satisfaction and costs of remifentanil patient controlled analgesia compared to epidural analgesia. The full design and outcome of the trial have been reported previously.[10,12] In short, the study showed that satisfaction with analgesia is lower in women randomised to remifentanil patient controlled analgesia with no differences in labour characteristics, neonatal outcome, maternal and neonatal admission or costs.[10, 13]

The aim of this sub analysis of the RAVEL trial was to report the detailed analysis of peripheral oxygen saturation (SpO2) and temperature, in women randomised to remifentanil patient controlled analgesia or epidural analgesia for labour analgesia.

Material and Methods

The RAVEL trial was a multicentre randomised controlled equivalence trial performed in 15 hospitals in the Netherlands within the structure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NTR 2551). Healthy women (American Association of Anaesthesiologists' classification 1 or 2), >17 years of age, with the intention to deliver vaginally were eligible to participate. Exclusion criteria were contra-indication for one of the treatments, hypersensitivity for one of the products used or labour <32 weeks gestation. We included women in secondary and tertiary care centres. After obtaining informed consent, women were randomised antepartum to remifentanil patient controlled analgesia or epidural analgesia for labour analgesia and only given pain relief during labour at their request. The trial was approved by the Central Committee on Research Involving Human Subjects and the Medical Ethics Committee of the Leiden University Hospital (p10-240) and the Boards of Directors of the participating centres.

Women who received remifentanil patient controlled analgesia were given 30 μg boluses of remifentanil with a lockout time of 3 minutes, no background infusion was allowed. It was possible to decrease the dose to 20 μg or increase to 40 μg if deemed necessary by the attending physician. Women who received epidural analgesia were treated according to the institutional locoregional analgesia protocol.

Primary outcome measure was satisfaction with pain relief. Secondary endpoints were pain intensity (AUC), satisfaction overall, labour characteristics, maternal and neonatal outcome and costs. Results of these analyses are reported previously.[10]

Maternal parameters were measured during administration of analgesia (temperature, and peripheral oxygen saturation (SpO2), measured by pulsoximetry). These were obtained and recorded once before the start of analgesia and at 15 minute intervals during the first hour of treatment followed by hourly recordings until delivery. Also minimum oxygen saturation, maximum temperature and occurrence of respiratory depression (<8 breaths/minute) were recorded as separate variables.

Maternal parameters were analysed until 11 hours after the start of analgesia. We calculated this time frame from the available data on duration of labour and analgesia.

Statistical analysis

Data were analysed on an intention to treat basis. Normally distributed data are presented as means with SDs; skewed distributions are presented as medians with interquartile range. For categorical data, the treatment effect is presented as relative risk with 95% confidence intervals. P-values were calculated with the χ^2 test, unless the expected cell count was less than 5, in which case we used the Fisher's exact test. For continuous data with a non-normal distribution, we used the Mann-Whitney U test. Calculation of the percentages was based on the number of valid observations. Maternal parameters, peripheral oxygen saturation and temperature, are reported as means for the whole duration of analgesia and means at the hourly recordings. To account for the correlated observations within persons, repeated measurement analysis, i.e. Linear Mixed Model analysis (LMM), was used to firstly examine the association between the type of analgesia and

time course of the peripheral oxygen saturation. We corrected for the peripheral oxygen saturation values before administration of analgesia (SpO2 at T0) and introduced an interaction term between analgesia and time of measurement, because the effect of analgesia on each time point can be different for each type of pain relief. Secondly, we determined factors that also could affect the peripheral oxygen saturation, i.e. age, BMI, pulmonary disease/medication and duration of labour and corrected additionally for these factors to study the independent effect of type of analgesia on peripheral oxygen saturation. We modelled the covariance matrix by starting with an unstructured covariance matrix and testing simpler matrices with the Restricted Maximum Likelihood test (REML) until a model was obtained that was as parsimonious as possible. The same strategy was applied to study the effect of type of analgesia on the course of the temperature: we corrected for the temperature before administration of analgesia (temp at T0) and introduced an interaction term between analgesia and time of measurement. Secondly, we determined factors that also could affect the temperature, i.e. age, >24 hours rupture of membranes, and use of antibiotics and corrected additionally for these factors to study the effect of type of analgesia on the temperature. The same strategy for finding the optimal covariance matric was followed as described above.
Statistical analysis was performed with SPSS version 20 (SPSS, Chicago, IL). $P<0.05$ was considered statistically significant.

Results

From May 30th 2011 until October 24th2012 1414 women were randomised of whom 51 women were excluded after randomisation because they delivered through elective caesarean section. There were three women lost to follow up and two women withdrew consent after randomisation; all in the epidural group. The flowchart and baseline characteristics of these women are reported elsewhere.[10] Pain relief was used in 448/709 (65%) in the remifentanil patient controlled analgesia group and 346/705 (52%) in the epidural analgesia group (RR 1.3, [95% CI 1.2 to 1.5]). In the remifentanil allocated group, 403 women received immediate remifentanil patient controlled analgesia of whom 53 converted to epidural analgesia, 41 women received immediate epidural analgesia and four received other opioids. In the epidural analgesia allocated group, 297 women received epidural analgesia of whom three subsequently received remifentanil patient controlled analgesia because of insufficient pain relief, 32 received immediate remifentanil patient controlled analgesia (of whom two women converted to epidural analgesia because of insufficient pain relief) and 17 received other opioids.

Since maternal parameters were only measured in women who received remifentanil patient controlled analgesia or epidural analgesia (and not in women who received other opioids), we included 444+329 women in this analysis. Of the 444 women allocated to remifentanil patient controlled analgesia, 403 women were treated with remifentanil and 41 with epidural analgesia. Of the 329 women allocated to epidural analgesia 297 were treated with epidural analgesia and 32

with remifentanil. Reasons for receiving other pain relief than according to randomisation outcome were reported previously.[10]

Baseline characteristics were comparable between groups except for parity (table 1).

Table 1. Baseline characteristics of women receiving analgesia. Intention to treat analysis.

Baseline characteristics	Remifentanil PCA N=444	Epidural analgesia N=329	p value
GA at randomisation (weeks; median [IQR])	38.1 [35.9-39.5]	37.9 [35.7-39.3]	0.53
Maternal age (years; means [SD])	31.3 [5.3]	31.5 [5.2]	0.71
Ethnic origin			
Caucasian	379 (85.7%)*	290 (88.7%)¶	0.23
Education			
≥higher education	186 (52.1%)ǁ	155 (54.6%)º	0.53
Body mass index (median [IQR])	24.3 [21.7-27.2]†	24.2 [21.7-28.1]‡	0.20
ASA classification			
ASA 1	319 (71.8%)	228 (69.3%)	0.44
ASA 2	125 (28.2%)	101 (30.7%)	
Parity			
0	231 (52%)	196 (59.6%)	0.04
≥1	213 (48%)	133 (40.4%)	
Multiple pregnancy	19 (4.3%)	11 (3.3%)	0.46

Data are n (%) unless otherwise indicated. *0.5% missing values (2 of 444 participants). ¶ 0.6% missing values (2 of 329 participants). ǁ 19.6% missing values (87 of 444 participants). º13.7% missing values (45 of 329 participants). †2.7% missing values (12 of 444 participants). ‡2.7% missing values (9 of 329 participants).

In the remifentanil allocated group a similar number of nulliparous and parous women received analgesia whereas in the epidural allocated group a significantly larger number of nulliparous women received analgesia. Median duration of analgesia was 4.5 hours with the 90th centile being 11 hours. As for labour characteristics and maternal and neonatal outcome there was a significant difference in time from request to start of analgesia, duration of analgesia and duration of second stage, all shorter in the remifentanil group (table 2). More women in the epidural allocated group were treated with antibiotics for suspicion of intrauterine infection (RR 0.7 [95% CI 0.48-1.0], p = 0.03).

Table 2. Labour characteristics of women receiving analgesia, intention to treat analysis.

	Remifentanil PCA N=444	Epidural analgesia N=329	RR (95% CI)	p value
Gestational age at delivery (weeks; median [IQR])	39.9 [38.6-40.9]	39.6 [38.4-40.9]		0.28
Onset of labor				
Spontaneous	150 (33.8%)	114 (34.7%)	0.98 (0.87 to 1.1)	0.80
Induced	294 (66.2%)	215 (65.3%)		
Dilatation at request pain relief (median [IQR]))	4 [3-5]	4 [3-5]		0.47
Fetal condition at start pain relief				
optimal	398 (90.2%)±	297 (90.3%)	1.0 (0.81 to 1.2)	0.99
Time from request to start analgesia (minutes, median [IQR])	28 [15-45]	55 [33-81]		<0.001
Duration of analgesia (minutes, median [IQR])	236 [128-376]	339 [183-454]		<0.001
Duration second stage of labour (minutes, median [IQR])	25 [11-51]	34 [15-59]		0.007
Meconium stained amniotic fluid	46 (10.4%)†	45 (13.7%)	0.87 (0.7 to 1.1)	0.17
Augmentation with oxytocin	292 (66.1%)†	237 (72%)	0.89 (0.79 to 1.0)	0.08
>24 hours ROM	30 (6.8%)†	28 (8.5%)	0.9 (0.69 to 1.2)	0.37
Suspected infection treated with antibiotics	16	23	0.7 (0.48 to 1.0)	0.03
Mode of delivery				
Spontaneous	308 (69.4%)	264 (68.1%)	1.0 (0.9 to1.2)	0.70
Vaginal instrumental	54 (12.2%)	45 (13.7%)	0.94 (0.78 to 1.1)	0.54
Caesarean section	82 (18.5%)	60 (18.2%)	1.0 (0.85 to 1.2)	0.98
Postpartum haemorrhage (≥1000 ml)	40 (9.1%)‡	27 (8.2%)*	1.1 (0.85 to 1.3)	0.66
Apgar score <7 neonate 1				
5 min	8 (1.8%)‖	9 (2.8%)º	0.82 (0.49 to 1.4)	0.36
Umbilical artery pH <7.10	18 (5.5%)¶	18 (6.9%)§	0.89 (0.64 to 1.2)	0.47
Major maternal complication	6 (1.4%)	6 (1.8%)	0.87 (0.49 to 1.5)	0.6
Maternal admission	292 (65.8%)	228 (69.3%)	0.94 (0.82 to 1.1)	0.3
Length of admission (days; median [IQR])	2 [1-3]	2 [1-3]		0.37
Neonatal admission	264 (59.5%)	198 (60.2%)	0.99 (0.87 to 1.1)	0.84
Length of admission neonate 1 (days; median [IQR])	2 [1-3]	2 [1-3]		0.24
Length of admission neonate 2 (days; median [IQR])	3 [2-5.75]	4 [3-5.5]		0.32

Overall mean oxygen saturation was lower in women randomised to remifentanil patient controlled analgesia compared to epidural analgesia with a higher percentage of women experiencing desaturations <92% (table 3). We divided the individual SpO2 at the hourly recorded intervals into four groups, 80-85%, 86-90%, 91-95% and >96% (figure 1,2). At the moments of these mandatory recordings no women had a SpO2 of <81%. These lowest scores were measured in between hourly mandatory recordings. Mean temperature was higher in women randomised to epidural analgesia with a significant difference in maximum recorded temperature above 38 °C (table 3).

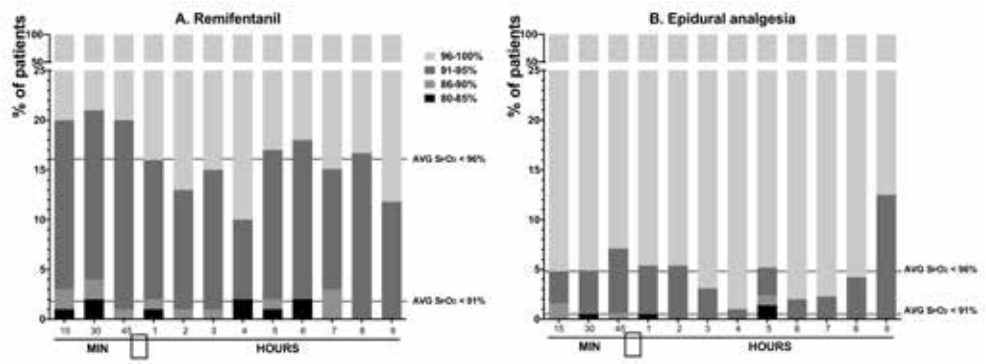

Figure 1,2. Mean oxygen saturation remifentanil patient controlled analgesia and epidural analgesia

Table 3. Maternal parameters in women receiving analgesia. Intention to treat analysis.

	Remifentanil PCA N=444	Epidural analgesia N=329	RR (95% CI)	p value	Missing N (%)
Temperature >38 °C during labour	35 (8%)	55 (17%)	0.65 (0.5-0.85)	<0.001	40 (9%)/29 (8.8%)
Saturation <92% (nr of patients)	71 (16%)	14 (4%)	1.5 (1.3-1.7)	<0.001	54 (12%)/59 (18%)
Respiratory depression (<8) nr of patients	4 (0.9%)	0	5.8 (0.31-107)		3 (0.4%)
Mean saturation	97.4%	98.2%		<0.001	57 (13%)/82(25%)
Mean temperature °C	36.8	37.0		<0.001	83 (19%)/69 (21%)

With repeated measurement analyses we found that type of analgesia did influence maternal peripheral oxygen saturation, with women randomised to remifentanil having a significantly lower peripheral oxygen saturation than the epidural group for nearly the whole studied period (estimate 0.99358 p=<0.001). Also, the peripheral oxygen saturation level was dependent on time of measuring/recording since start of analgesia (p = <0.001). Furthermore, the statistically significant interaction term of type of anaesthesia and time, showed that effect of remifentanil on peripheral oxygen saturation over time differed from the effect of epidural analgesia over time (p =<0.001).
We found that type of analgesia influenced the maternal temperature, with maternal temperature being significantly lower in the remifentanil group compared to the epidural analgesia group (estimate -0.286099, p<0.001). Also, the maternal temperature level was dependent on time of

measuring/recording since start of analgesia (p = <0.001). No interaction was found for type of analgesia and time, this was corrected for >24 hours rupture of membranes but not for use of antibiotics because the numbers were too small. (Table 4,5) (Figure 3,4).

Table 4. Estimates of Fixed Effects maternal SpO2.

Parameter	Estimate	p value	95% Confidence interval	95% Confidence interval2
			Lower Bound	Upper Bound
Intercept	62,666	0.84	-180990,920	181116,253
Remifentanil PCA	-0,994	<0.001	-1,242	-0,745
Epidural analgesia	ref			
Time of recording	-0,026	<0.001	-0,032	-0,020
Remifentanil PCA * moment of recording	0,04	<0.001	0,036	0,045
Epidural analgesia * moment of recording	ref		.	
No pulmonary medication	-0,045	0.92	-0,942	0,852
No pulmonary disease	0,049	0.91	-0,835	0,933
BMI	-0,01	0.93	-913,770	913,750
Duration of labour	-0,011	0.29	-0,035	0,013
Age	-0,026	0.99	-226,032	225,981
Maternal SpO2 before analgesia	0,373	0.84	-1540,409	1541,156

Table 5. Estimates of Fixed Effects maternal temperature.

Parameter	Estimate	p value	95% Confidence interval	95% Confidence interval2
			Lower Bound	Upper Bound
Intercept	14,802	<0.001	12,191	17,413
Remifentanil PCA	-0,286	0.002	-0,468	-0,104
Epidural analgesia	ref			
Time of recording	0,107	<0.001	0,087	0,128
Remifentanil PCA * moment of recording	-0,003	0.853	-0,032	0,027
Epidural analgesia * moment of recording	ref			
<24 hours ROM^	-0,106	0.22	-0,276	0,064
>24 hours ROM^	0b			
Maternal temperature before analgesia	0,593	<0.001	0,523	0,664
^Rupture of membranes				

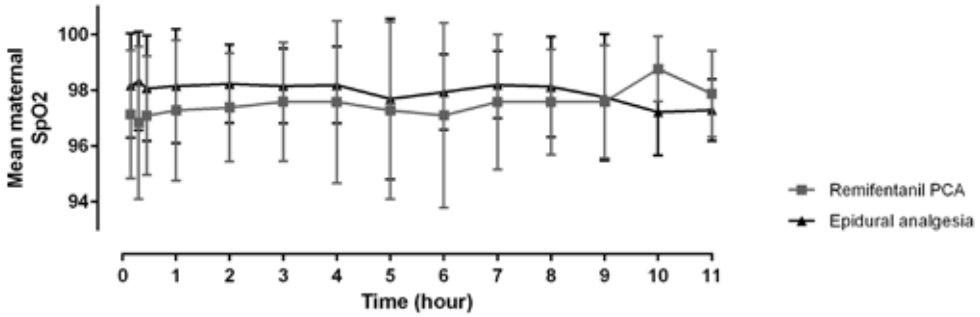

Figure 3. Time course of peripheral maternal oxygen saturation.

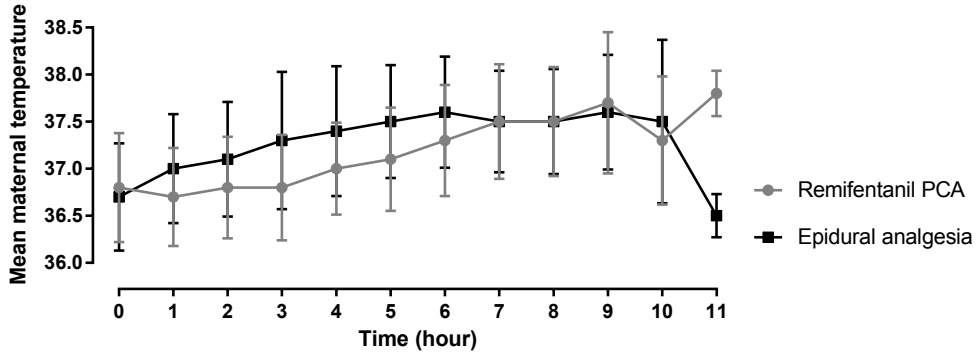

Figure 4. Time course of maternal temperature.

Three women in the remifentanil group who received remifentanil as analgesia had one episode of a respiratory rate of <8, one woman had two episodes. Two of those women also had a lowest recorded SpO2 of <92% (64% and 88% respectively) for which they were treated with supplementary oxygen. In all women the respiratory rate improved without discontinuing remifentanil. Data on respiratory rate were available in 364 of 444 women. No respiratory depressions were recorded in the epidural analgesia group (248 no recorded respiratory depression, 99 recorded unknown).

Discussion

Respiratory complications are a serious threat in women receiving remifentanil as analgesia during labour as is an increased temperature with more women and neonates treated for suspicion of sepsis in women receiving epidural analgesia.[1,11] Because of this we decided to perform a separate and more detailed analysis of maternal peripheral oxygen saturation and temperature from the data available from the RAVEL trial. We found that the peripheral oxygen saturation in women on remifentanil patient controlled analgesia was significantly lower than in women on epidural analgesia. This finding persisted throughout labour and was not limited to a specific moment after

the start of analgesia. We also showed that maternal temperature was significantly higher in women in the epidural analgesia group, with a higher incidence of fever (temperature >38°C), and that this persisted throughout labour. Our findings are in agreement with the results of previous studies.[5,14-18]

We showed that there is a difference in maternal oxygen saturation with intermittent recording of measurements but shorter episodes of desaturation in between recordings could have been missed. A study performed by Douma et al showed that 68% and 38% of women treated with remifentanil patient controlled analgesia had an episode of SpO2 <92% for >1 and > 2 minutes, respectively.[5] These findings prove that there is not only a significant difference in oxygen saturation but also a clinically relevant difference. Even with strict surveillance and continuous monitoring of oxygen saturation, it is possible that not all desaturations were noticed by attending personnel. This stresses the need for continuous one to one monitoring of women who use remifentanil patient controlled analgesia. We also showed that desaturation is not limited to a certain time frame, for example the first hour after start of analgesia, making strict surveillance necessary for the whole time a woman is treated with remifentanil. This is also emphasized in several papers describing adverse respiratory events.[19-22]

A significant difference in temperature was found with higher maternal temperature in the epidural analgesia group. In our study 17% (55/329) of women developed a fever (temperature >38°C) in the epidural analgesia group compared to 8% (35/444) women in the remifentanil group. This difference is not only statistically significant but also clinically relevant since more women were treated with antibiotics for suspicion of intrauterine infection. Our findings are in concurrence with the incidence of fever found by Philip et al[3] who found that 15% of women receiving epidural analgesia developed a fever and the incidence of fever in women on remifentanil of 10% found by Douma et al[5].

The difference in temperature disappeared at seven hours, while the difference in maternal SpO2 disappeared at nine hours with even lower scores in the epidural group. The most plausible explanation for both is that there were not enough recordings from seven-eight hours onward to demonstrate a difference. From zero to seven hours there were around 25% missing scores. At 11 hours this percentage increased to 90%. Another explanation for the increase in temperature in the remifentanil group is that a percentage of these women converted to epidural analgesia.

Strength of this study is the fact that it is a large randomised controlled trial with prospective collection of data, that was performed in 15 centres within the well-organised structure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. Maternal parameters were prospectively collected in all women receiving analgesia during the whole period in which analgesia was administered, making our data representative for daily practice. Also, ours is one of the biggest studies comparing remifentanil patient controlled analgesia with prospective collection of maternal parameters. Furthermore, not all other published studies analysed and reported on maternal oxygen saturation and temperature in detail.

One limitation is the percentage of missing SpO2 data in women on epidural analgesia. SpO2 was initially recorded in 80% of women on remifentanil but only 60% of women on epidural analgesia. Although this is a limitation in the comparison of both treatments the aim was to analyse effect of remifentanil on maternal oxygen saturation and there were sufficient data to report on this outcome. Previous studies show that epidural analgesia does not affect maternal SpO2.[5,11] The aim of this secondary analysis was to report on maternal SpO2 in women using remifentanil patient controlled analgesia during labour and to add to the knowledge about respiratory complications of women on remifentanil. Because of the randomised nature of the original trial we also reported data of women using epidural analgesia, even with the larger number of missing data in this group.
Another limitation is that it did not prove feasible to monitor maternal peripheral oxygen saturation continuously to analyse frequency and duration of episodes of desaturation as described above.

Conclusion

Epidural analgesia is associated with a greater incidence of fever and significantly higher temperature overall. Remifentanil patient controlled analgesia has an effect on maternal SpO2 with significantly lower mean SpO2 during the labour period. The effect on time course of oxygen saturation differs between remifentanil and epidural analgesia. We also saw more desaturation episodes <92% in the remifentanil group. This shows that respiratory complications are a serious problem associated with remifentanil and that continuous monitoring by trained personnel is advised.

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7

Safety of remifentanil during labour: a systematic review and meta-analysis

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Submitted

Abstract

Background: Remifentanil has a unique pharmacological profile, which makes the opioid suitable for labour analgesia. We performed a systematic review and meta-analysis of side effects and safety of intravenous remifentanil administered for labour analgesia.

Methods: Pubmed, EMBASE and Cochrane Library databases were searched for randomised controlled and observational trials that compared side effects of remifentanil to any other labour analgesic. The primary outcome was incidence of oxygen saturation (SpO_2) less than 95% in parturients during treatment with remifentanil. Secondary outcomes included other maternal side effects and effects on the neonate.

Results: Sixteen trials were identified for inclusion comparing remifentanil to epidural analgesia (EA) or remifentanil to another opioid, either fentanyl or pethidine. Compared to EA remifentanil treatment was associated with a higher risk of saturation levels below 95% (RR 3.12, 95% CI 2.37-4.11), while compared to fentanyl or pethidine the risk was similar (n = 162; RR 1.57, 95% CI 0.95-2.61). Of the secondary outcomes remifentanil caused more nausea and sedation than EA. Other outcomes did not differ between treatments.

Conclusion: While remifentanil was comparable to other opioids with respect to maternal and neonatal outcomes, compared to epidural analgesia more toxicity was seen, in particular more oxygen desaturations and sedation. These results indicate that the safety of epidural analgesia is superior to that of remifentanil in labour analgesia.

Introduction

Over the last two decades intravenous remifentanil has become an increasingly popular method for labour analgesia. This is related to remifentanil's unique pharmacokinetic profile with a short terminal half-life due to hydrolysis by non-specific blood and tissue esterases, and consequently a metabolism independent of renal and/or kidney function.[1] Remifentanil crosses the placenta but is rapidly metabolised by the fetus rendering it suitable analgesia during labour.[2] Moreover, remifentanil's rapid onset of action with short latency to peak effect and its rapid offset make remifentanil very suitable for patient-controlled analgesia (PCA). There have been multiple trials on the efficacy of remifentanil PCA (RPCA) during labour. The literature suggests that although remifentanil appears superior in reducing pain scores relative to other opioids such as pethidine,[3-9] compared to epidural analgesia (EA) efficacy seems inferior.[10-12]

While the popularity of remifentanil as labour analgesic increases, the safety of the opioid has not been fully established yet. As remifentanil is a potent opioid, the major concerns regarding the use of remifentanil during labour are respiratory depression and desaturation. Indeed, several studies show lower saturation scores and more periods of desaturation[3, 10, 12, 13] and five recent case reports describe serious incidents during administration of remifentanil on the labour ward; in three cases a respiratory arrest occurred while in two cases a cardio-respiratory arrest was described.[14-18] Besides respiratory complications, other side effects such as sedation and nausea during use of remifentanil are frequently mentioned.
In order to get a complete picture of the maternal and neonatal adverse events of remifentanil administered for labour analgesia relative to other available analgesia modalities, we performed a systematic review and meta-analysis of remifentanil toxicity in its treatment of labour pain.

Methods

Search strategy

Two authors (MD, LF) conducted a systematic search for randomised controlled trials and observational studies, in the search engines PubMed, EMBASE and Cochrane Library. The last search was performed on October 1st, 2015. Keywords that were used included remifentanil, labour and obstetric analgesia. No limitations were used concerning publication date. The references of all retrieved articles were examined for other publications. The detailed search strategy for all databases can be obtained from the authors.

Inclusion and exclusion criteria

All randomised controlled trials and observational studies that compared efficacy and side effects of remifentanil with any other labour analgesic modality were included. Studies that were considered had to contain clinical data on maternal side effects (*e.g.*, respiratory depression, hypotension,

nausea, pruritus, sedation) and a clear description of how these data were collected. The full text article had to be available and only articles written in English language were included. Two authors (MD, LF) retrieved eligible articles and excluded irrelevant trials. Any discrepancies during data extraction were resolved by consulting a third author (AD). We choose not to restrict our analyses to randomised controlled trials but also to include observational studies as our aim was to review side effects of remifentanil and observational studies are suitable for the review of such data.

Outcome measures

The primary outcome was the incidence of oxygen saturation (SpO_2) less than 95% in parturients during treatment with RPCA. For parturients, secondary outcomes included SpO_2 less than 90%, low respiratory rate (<9 breaths min^{-1}), sedation, incidence of nausea and/or vomiting, hypotension, pruritus, conversion to other analgesia techniques and mode of delivery (instrumental, caesarean section). Additional secondary outcomes obtained from the neonate included fetal heart rate changes (as defined by author), acidosis (as defined by cord blood arterial pH less than 7.10), Apgar scores less than 7 at 5 minutes and naloxone administration. Three comparators were used in this review; other opioids (fentanyl or pethidine), epidural analgesia and nitrous oxide.

Validity assessment

Quality assessment of included randomised controlled trials was performed by two authors (MD, LF). For randomised controlled trials the risk of bias tool of the Cochrane Handbook for Systematic Review of Interventions was used. The following items were assessed: 'random sequence generation', 'allocation concealment', 'blinding of participants', 'blinding of clinical staff', 'blinding of outcome assessors', 'incomplete outcome data', 'selective outcome reporting', 'other bias'.

Statistical analysis

Relative risk, standard error and 95% were calculated based on 2x2 tables extracted from the articles**.** In case of zero events in one of the groups, ½ was added to entries in the 2x2 tables. Since considerable heterogeneity was expected, meta-analysis of the relative risks was performed using the standard random effects method of DerSimonian and Laird[19] using the program Metan of Stata/SE 13.1 for Windows, Statacorp LP, Texas.

Results

The search strategy resulted in 374 papers. After removal of duplicates and screening of titles and abstracts, 26 papers were further assessed in full for eligibility (Fig. 1). Of these, ten papers were excluded for reasons of low quality and improper study design, leaving 16 articles involving 3670 women that were included in the meta-analysis.

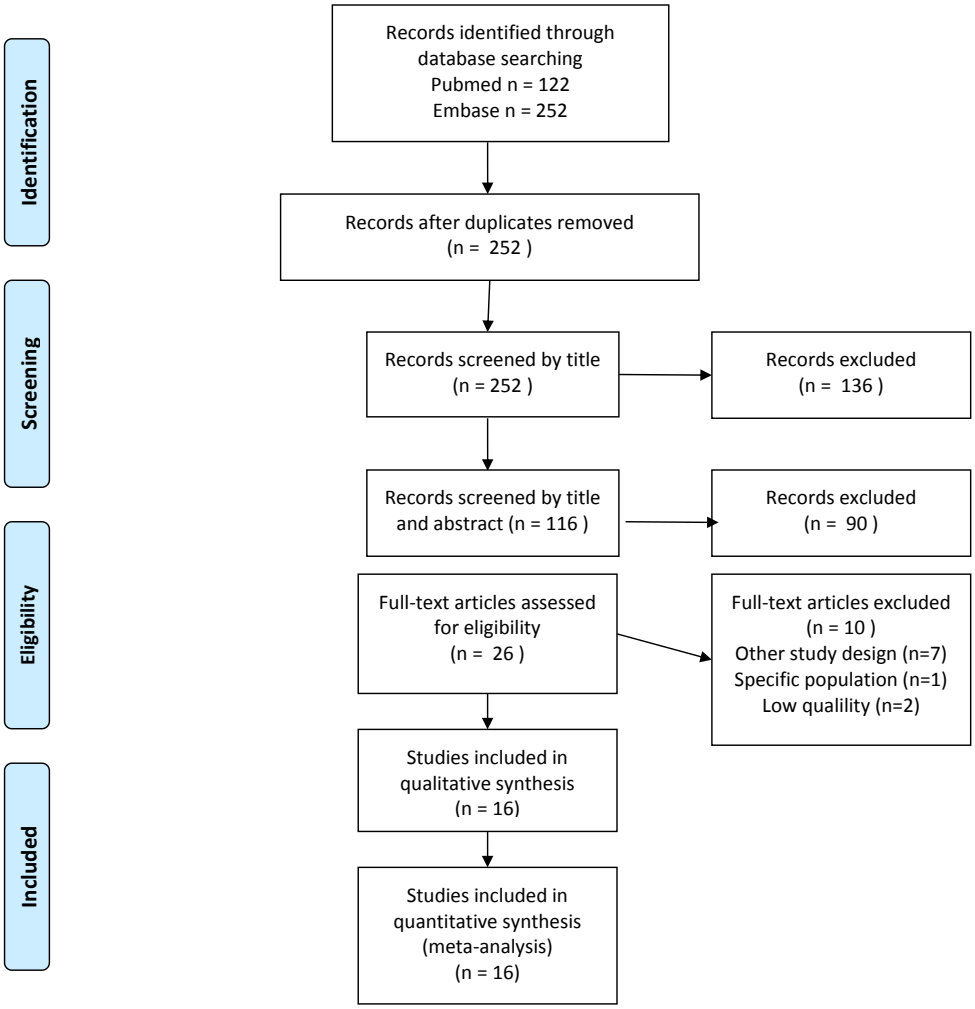

Figure 1. Flow diagram

Table 1 shows an overview of all included trials. Of the 16 studies, 14 trials were randomised controlled trials,[3, 5-8, 10-13, 20-24] and 2 were observational studies.[25, 26]

Remifentanil vs. other opioids. In seven trials remifentanil was compared to other opioid analgesics, of which in 6 trials remifentanil was compared to pethidine and the remainder to fentanyl. A total of 162 parturients received remifentanil, 163 parturients received pethidine and 105 were treated with fentanyl. One of the studies consisted of 3 arms, comparing remifentanil to pethidine and fentanyl.[3]

Table 1. Characteristics of included trials.

Reference	Year	Intervention/comparison	*n*	Analgesia regimens	Background infusion	Outcomes
Volikas et al.[6]	2001	Remifentanil PCA	9	Bolus 0.5 μg kg^{-1}; lockout 2 min	No	6,8,9,10,11,12,13
		Pethidine PCA	8	Bolus 10 mg; lockout 5 min		
Thurlow et al.[5]	2002	Remifentanil PCA	18	Bolus 20 μg; lockout 2 min	No	1,3,5,8,9
		Pethidine IM	18	100 mg		
Blair et al.[22]	2005	Remifentanil PCA	20	Bolus 40 μg; lockout 2 min	No	4,10,12,13
		Pethidine PCA	19	Bolus 15 mg; lockout 10 min		
Evron et al.[7]	2005	Remifentanil PCA	43	Bolus 0.27-0.93 μg kg^{-1}; lockout 3 min	No	1,4,5,7,8,9,10,12
		Pethidine IV	45	75 mg in 100 mL saline, up to max 200 mg		
Douma et al.[3]	2010	remifentanil PCA	52	Loading dose 40 μg; bolus 40 μg; lockout 2 min	No	1,4,5,7,8,9,10,11,12,13
		Pethidine PCA	53	Loading dose 49.5 mg, bolus 5 mg; lockout 10 min		
		Fentanyl PCA	54	Loading dose 50 μg, bolus 20 μg; lockout 5 min		
Shahriari et al.[8]	2007	Remifentanil IV	20	Bolus administered by anesthesiologist 25-50 μg; lockout 4 min	No	1,12
		Pethidine IM	20	1 mg kg^{-1}, max dose 200 mg per 4 hours		
Volmanen et al.[11]	2008	Remifentanil PCA	24	Bolus 0.1–0.9 μg kg^{-1}; lockout 1 min	No	4,5,8,10
		Epidural analgesia	21	20 mL levobupivacaine 0.625 mg mL^{-1} with fentanyl 2 μg mL^{-1}, manual bolus		
Douma et al.[10]	2011	Remifentanil PCA	10	Bolus 40 μg; lockout 2 min	No	4,5,6,7,8,9,10,11,12,13
		Epidural analgesia	10	Loading dose 12.5 mL 0.2% ropivacaine ropivacaine 0.1% with sufentanil 0.5 μg mL^{-1} continuous infusion		
Tveit et al.[13]	2012	Remifentanil PCA	17	Bolus 0.15 μg kg^{-1}, increasing dose steps 0.15 μg kg^{-1}, no max; lockout 2 min	No	3,4,5,6,7,8,9,10,11,12,13
		Epidural analgesia	20	Loading dose 15 mL ropivacaine 1mg mL^{-1} with fentanyl 2 μg mL^{-1}, continuous infusion		

Stocki et al.[12]	2013	Remifentanil PCA	19	Bolus 20-60 µg; lockout 2 min	No	1,3,4,5,7,8,9,12
		Epidural PCA	20	Loading dose 15 mL 0.1% bupivacaine with 50 µg fentanyl followed by PCA infusion of 0.1% bupivacaine with 2 mcg mL^{-1} fentanyl: basal infusion 5 mL h^{-1}, PCA bolus 2 mcg mL^{-1}; lockout 20 min		
Douma et al.[20]	2015	Remifentanil PCA	49	Bolus 40 µg; lockout 2 min	No	1,2,3,4,5,6,7,8,9,10,11,12,13
		Epidural analgesia	49	Loading dose 12.5 mL 0.2% ropivacaine ropivacaine 0.1% with sufentanil 0.5 µg mL^{-1} continuous infusion		
Freeman et al.[23]	2015	Remifentanil PCA	687	Bolus 20-40 µg; lockout 3 min	No	1,3,5,6,7,8,9,10,11,12,13
		Epidural analgesia	671	Local protocol		
Ismail et al.[24]	2011	Remifentanil PCA	380	Bolus 0.1-0.9 µg kg^{-1}; lockout 1 min	No	5,7,8,12,13
		Epidural analgesia	380	Loading dose 8 ml 0.125% levobupivacaine with fentanyl 2 µg mL^{-1} continuous infusion		
Volmanen et al.[21]	2005	Remifentanil PCA	15	Bolus 0.4 µg kg^{-1}; lockout 1 min	No	1,3,4,5,7,10
		Nitrous oxide	15	Local protocol		
Lin et al.[25]*	2014	Remifentanil PCA	170	Bolus 0.4 µg kg^{-1}; lockout 5 min Background infusion 0.04-0.05 µg kg^{-1} min^{-1}	Yes	2,3,4,5,7,8,10,11
		Epidural PCA	200	Loading dose 10 mL 0.068% ropivacaine with sufentanil 0.3 µg ml^{-1} followed by maintenance dose at 8 mL h^{-1}, PCA bolus 5 mL; lockout 15 min		
Marwah et al.[26]*	2011	Remifentanil PCA	47	Bolus 0.25 µg kg^{-1}; lockout 2 min Background infusion 0.025-0.05 µg kg^{-1} min^{-1}	Yes	1,2,4,5,6,7,8,9,12,13
		Fentanyl PCA	51	Bolus 25-50 µg; lockout 3 to 6 min	No	

PCA patient-controlled analgesia. Outcomes reported: 1. SpO2<95%; 2. SpO2<90%; 3. Respiratory rate<9; 4. Sedation; 5. Nausea/Vomiting; 6. Hypotension; 7. Pruritus; 8. Type of delivery; 9. Conversion rate to other analgesia 10. Fetal heart rate changes; 11. Acidosis; 12. Apgar score <7; 13. Naloxone use. * Observational study.

Remifentanil vs. epidural analgesia. Eight trials compared remifentanil to EA: 1356 parturients received remifentanil, 1371 parturients received EA.[10-13, 20, 23-25] Two of these trials consisted of 3 arms. One of these studies compared remifentanil to EA (360 patients) and to CSE (360 patients).[24] Data of the CSE group were not included in the analyses. The second trial was a two-arm randomised controlled trial with a third-arm observational cohort (the 'control group').[20] Only data of the randomised groups were included in this review. The administered local anaesthetic in the epidurals consisted of bupivacaine, levobupivacaine or ropivacaine combined with either fentanyl or sufentanil.

Remifentanil PCA vs. nitrous oxide. One study included in this review used nitrous oxide (N_2O; *n* = 15 parturients) as a comparator to remifentanil PCA, in a randomised cross-over model.[21]

In all trials a clear description of maternal data was given. An overview of measurements and monitoring is shown in table 1. In all studies remifentanil was administered via a patient-controlled on demand system, with the exception of 1 study, in which remifentanil was given intravenously on demand by an anaesthesiologist.[8] Different dose schedules were used, as is shown in table 1. Only 2 studies used a background infusion of remifentanil, both were observational studies.[25, 26] Details of risk of bias assessment are shown in figure 2. Overall, the included randomised trials had low risk of bias.

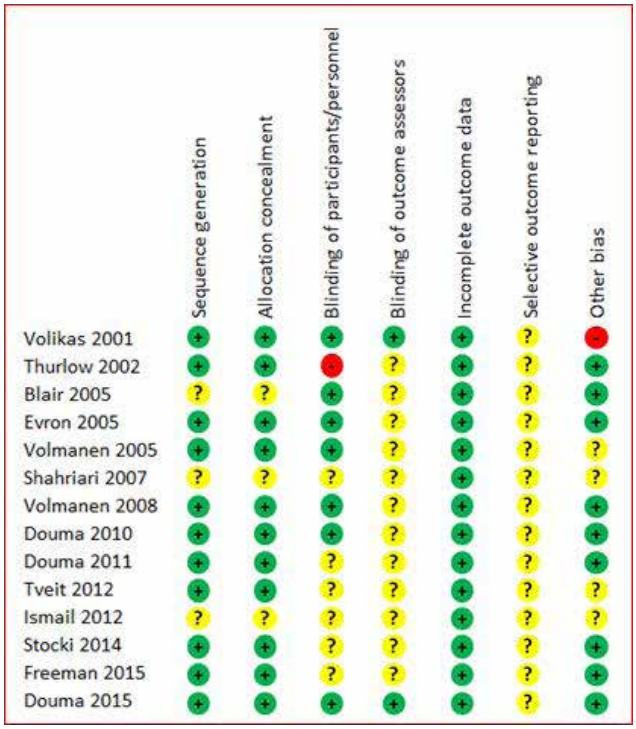

Figure 2. Risk of bias assessment.

Primary outcome

Maternal oxygen saturation less than 95% (Fig. 3).

In five trials, the risk of developing maternal saturation <95% was assessed in parturients receiving an opioid (remifentanil, pethidine or fentanyl). There was no difference in incidence of saturation below 95% between patients treated with remifentanil (187 women) or any of the other opioids (243 women) (RR 1.57 95% CI 0.95-2.61, Fig 3). [3, 5, 7, 8, 26] In contrast, parturients on RPCA (515 women) had a higher risk of desaturation incidents compared to women on EA (416 women): RR 3.12, 95% CI 2.37-4.11, Fig 3. Of the three studies analysed, one study was included that used 94% rather than 95% as a cut-off for desaturation.[12]

No significant difference was found in the N_2O study, in which 15 women completed the study. Two parturients in the remifentanil and one in the N_2O group experienced short (<1 min) desaturations (RR 1.67, 95% CI 0.25-11.12).[21]

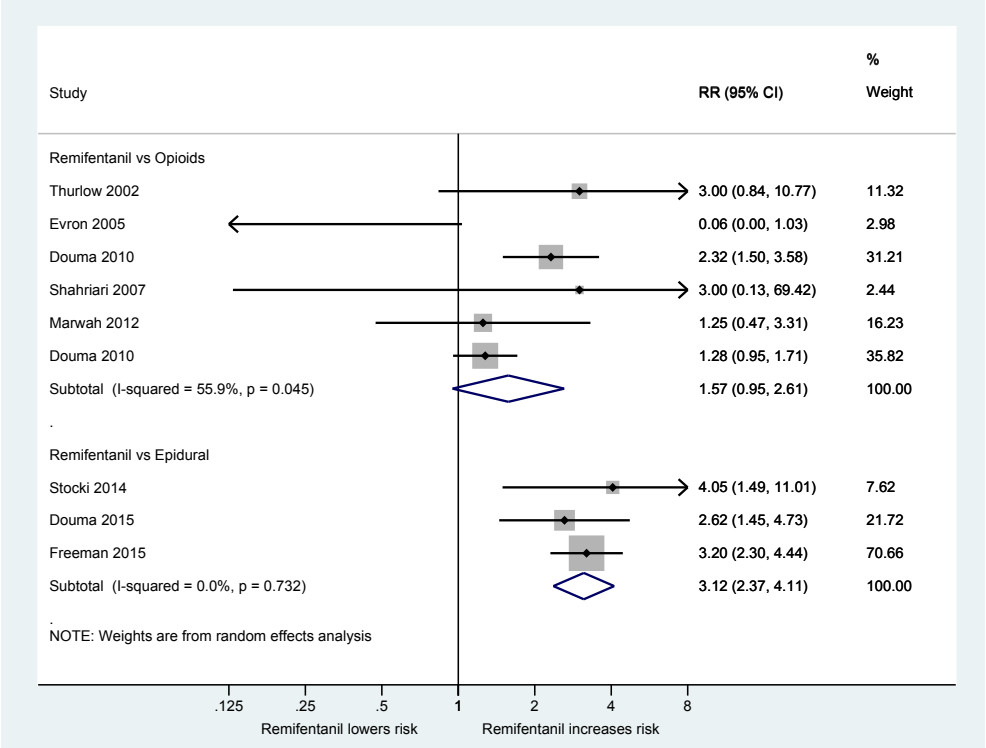

Figure 3. Number of parturients with oxygen desaturation < 95% in women receiving remifentanil versus other labour analgesics.

Secondary outcomes

Maternal desaturation below 90%. Only three trials, involving 566 women, investigated the incidence of SpO_2 < 90%, therefore we were not able to pool data. In one retrospective study RPCA (47 women) was compared to fentanyl PCA (51 women). No difference was found in SpO2 < 90% between RPCA and fentanyl (RR 4.70, 95% CI 0.83-26.53).[26] Two trials comparing RPCA

to EA reported the incidence of SpO2 < 90%. One trial reported zero parturients with SpO_2 < 90%, irrespective of treatment.[25] In contrast, Douma et al. described that women on RPCA had a significantly increased risk for desaturations below 90% compared to EA (19/40 vs 5/34, RR 3.02 95% CI 1.32–6.93).[20] One serious adverse event was reported in this study with oxygen saturation of 71% in combination with low respiratory rates (average 5 breaths min^{-1}).

Low respiratory rate. Only 1 trial, in which RPCA was compared to another opioid, investigated the risk on developing respiratory rates < 9 min^{-1}. More women in the RPCA group had respiratory rates of less than 8 min^{-1} compared to the pethidine group (3/18 vs 0/18).[5] Compared to EA no statistically different risk was found between treatments (RPCA 994 women, EA 964 women; RR 1.08, 95% CI 0.63-1.83).[12, 13, 20, 23, 25] Of these five studies, four studies found little to no significant effect on respiratory rates. This in contrast to one study, which found low respiratory rates in both groups.[12] None of the parturients in the N_2O study (15 women) suffered from low respiratory rates below 9 min^{-1}, irrespective of treatment.[21]

Sedation. Twelve trials, involving 1048 women, reported this outcome, but due to variations in the scoring method for sedation among trials, it was not possible to pool the data. In 5 trials comparing remifentanil to another opioid, the risk of sedation was assessed.[3, 7, 8, 22, 26] Three trials (RPCA 87 women, other opioids 90 women) found no difference in sedation scores.[8, 22, 26] One trial found higher sedation scores (RPCA 52 women, other opioids 107 women) in contrast to another trial, which found lower sedation scores (RPCA 43, pethidine 45 women) in parturients treated with remifentanil.[3, 7] On the contrary, four studies found significantly more sedation in parturients receiving RPCA (260 women) compared to EA (290 women). [11, 13 20, 25] Two trials reported no significant differences between RPCA and EA.[10, 12] Women receiving N_2O (15 parturients), showed significantly higher sedation scores scores.[21]

Nausea (Fig. 4). The risk of developing nausea was similar in patients receiving remifentanil to any of the other opioids (4 trials; RPCA 160, other opioids 221 women; RR 0.89, 95% CI 0.66-1.21).[3, 5, 7, 26] In contrast, patients on RPCA had a higher risk of developing nausea compared to EA (8 trials; RPCA 1112; EA 1045 women; RR 1.56, 95% CI 1.25-1.95; Fig 4).[10-13, 20, 23-25] No significant difference was detected in the N_2O study (RR 1.18 95% CI 0.48-2.88).[21]

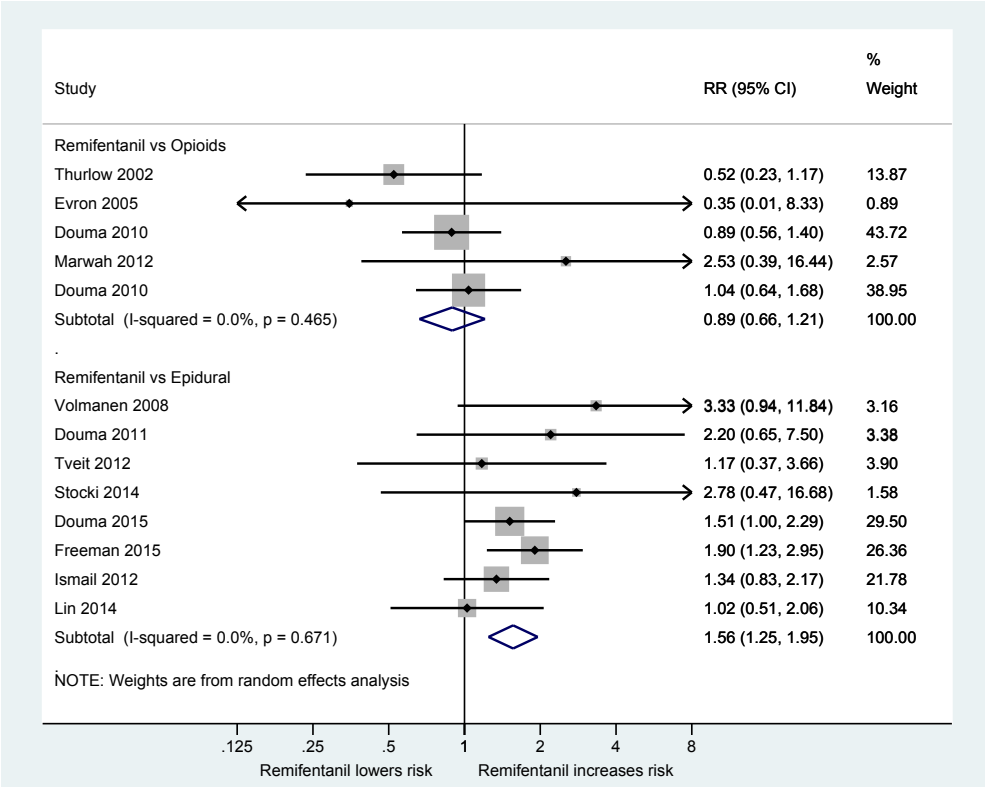

Figure 4. Number of parturients developing nausea/vomiting during remifentanil versus other labour analgesics.

Hypotension. Compared to other opioids, RPCA had no additional risk for hypotension (2 trials; RPCA 56, other opioids 58 women, RR 1.92 (0.17-21.97).[6, 26] In contrast, EA carried a greater risk for hypotension (4 trials; RPCA 523, EA 426 women, RR 0.60, 95% CI 0.39-0.95).[10, 13, 20, 23]

Pruritus (Fig. 5). Women on RPCA had a greater risk for pruritus than parturients on other opioids (3 trials; RPCA 141 women, other opioids 197 women, RR 2.32, 95% CI 1.08-5.02).[3, 7, 26] Compared to EA the risk was comparable (7 trials; RPCA 1088, EA 1024 women, RR 0.82, 95% CI 0.55-1.21),[10, 12, 13, 20, 23-25] as well as for N_2O (1 trial, 15 women, RR 1.67, 95% CI 0.25-11.12).[21]

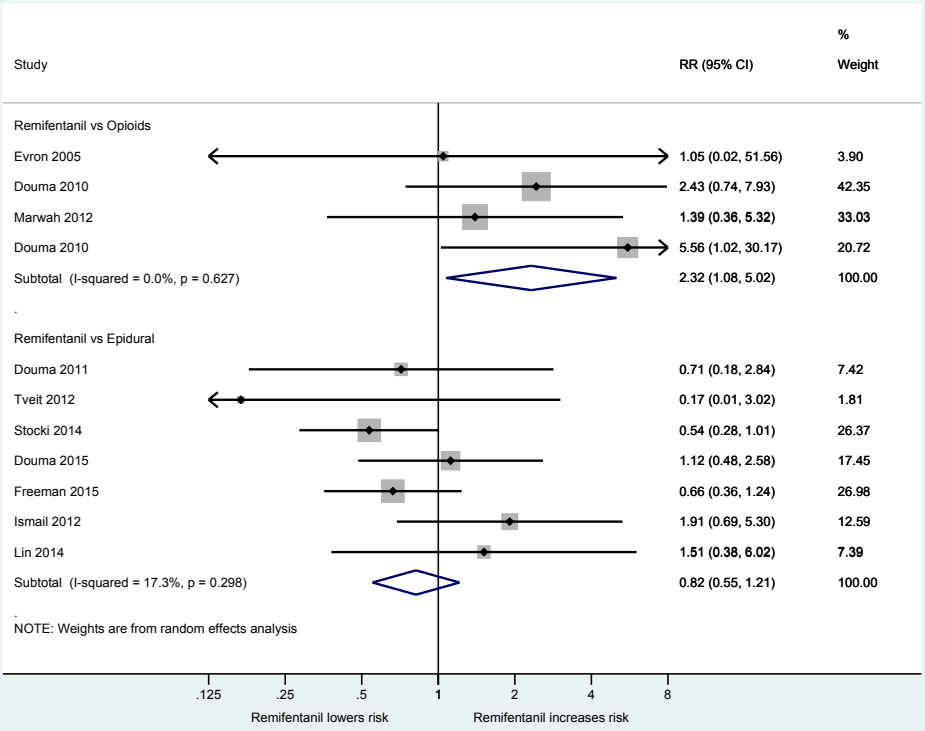

Figure 5. Pruritus in parturients receiving remifentanil versus other labour analgesics.

Mode of delivery: Instrumental delivery and caesarean section (Figs. 6 and 7).
Compared to other opioids, there was no significant difference in the incidence of instrumental delivery (5 studies; RPCA 161, other opioids 203 women, RR 1.22, 95% CI 0.74-2.02) or caesarean section (5 studies; RPCA 161, other opioids 203 women, RR 1.58, 95% CI 0.87–2.89).[3, 5-7, 26] Similar observations were made in the comparisons to EA for instrumental delivery (8 studies; RPCA 1373, EA 1416 women, RR 0.93, 95% CI 0.74-1.17) and caesarean section (8 studies; RPCA 1373, EA 1416 women, RR 0.84 95% CI 0.65-1.09) in women receiving remifentanil.[10-13, 20, 23-25]

Conversion to epidural analgesia. In 5 studies, involving 398 women, RPCA was compared to other opioids.[3, 5-7, 26] Treatment with remifentanil and other opioids have a similar conversion rate to EA (RR 0.68, 95% CI 0.38-1.22).

Fetal heart rate. Nine studies, involving 859 women reported this outcome. Because of different scoring methods, it was not possible to pool the data. Only 1 out of 3 studies comparing RPCA to an opioid found significantly less abnormal fetal heart rate (FHR) patterns and less fetal heart rate decelerations in parturients receiving remifentanil compared to pethidine.[7] The 5 trials comparing RPCA to EA reported no differences. [3, 10, 11, 20, 25] Furthermore, compared to nitrous oxide, no significant differences were found.[21]

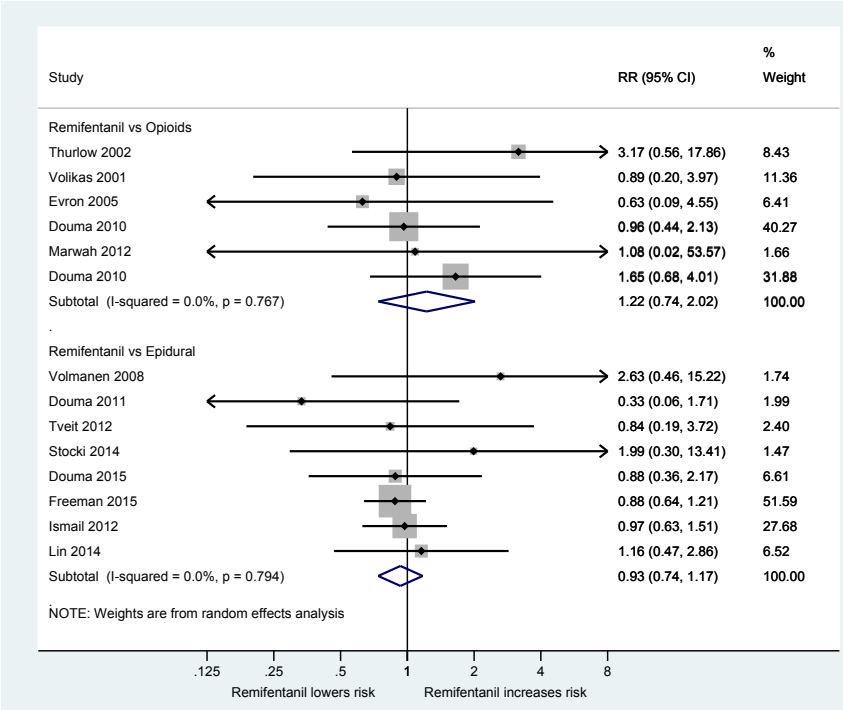

Figure 6. Instrumental delivery in parturients receiving remifentanil versus other labour analgesics.

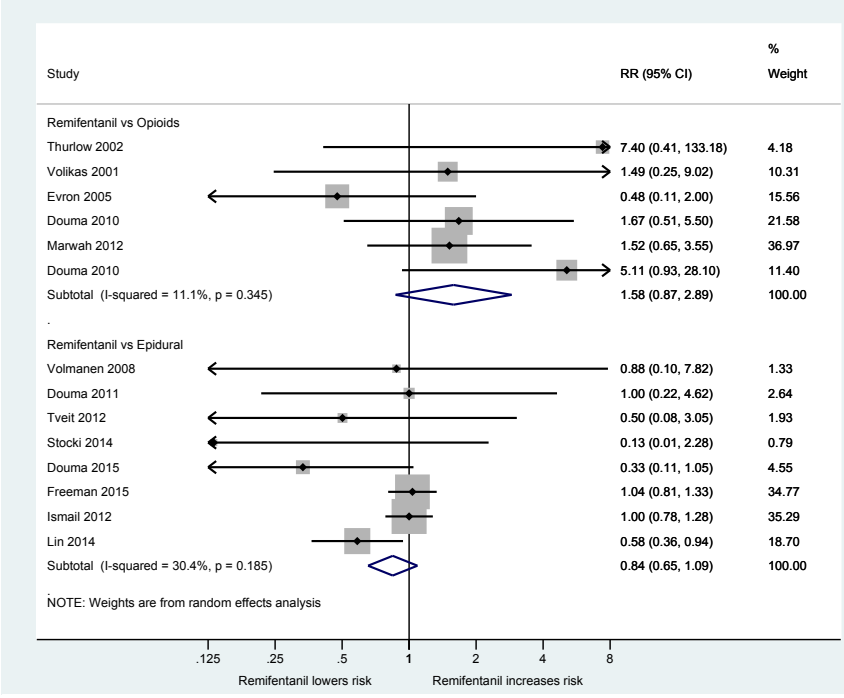

Figure 7. Caesarean section in parturients receiving remifentanil versus other labour analgesics.

Apgar score < 7 (Fig. 8). There was no evidence of a significant difference between RPCA and other opioids (5 studies; remifentanil 168, other opioids 224 women, RR 0.60 95% CI 0.22-1.65).[3, 6-8, 26] Compared to EA, no statistically significant difference was found (6 studies; RPCA 1162, EA 1150 women, RR 0.88, 95% CI 0.51-1.50, Fig. 8).[10, 12, 13, 20, 23, 24]

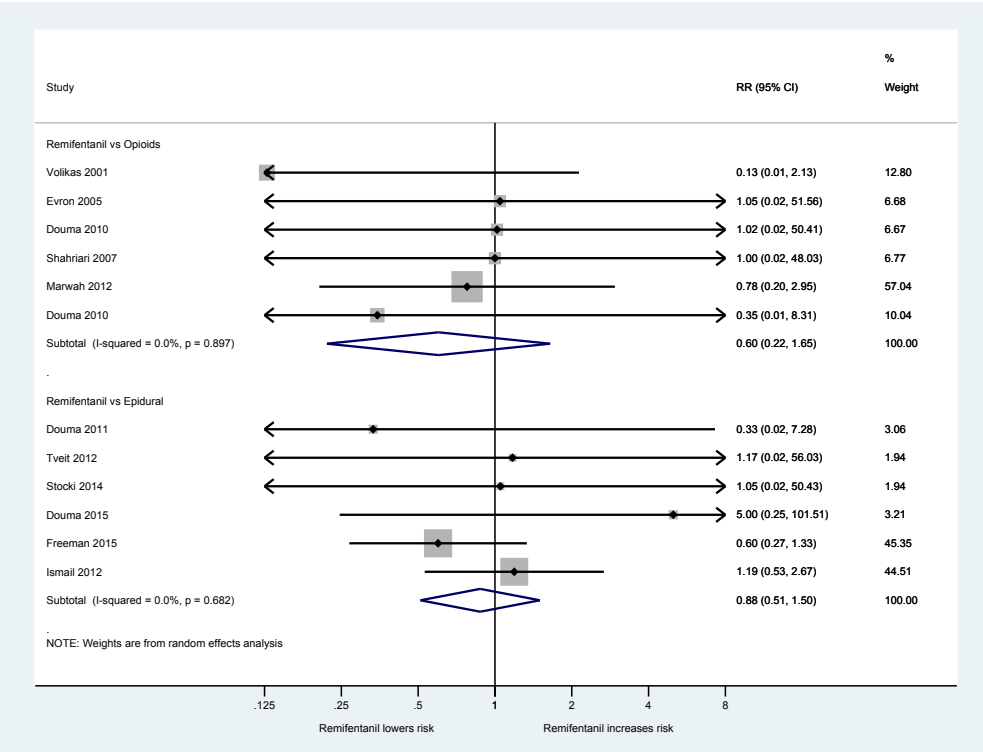

Figure 8. Number of Apgar scores <7 in neonates of which mothers received remifentanil versus other labour analgesics.

Umbilical cord acidosis. In 2 trials the risk of developing an umbilical cord blood arterial pH less than 7.10 was assessed with similar risks in parturients receiving RPCA or any of the other opioids (RPCA 67, other opioids 119 women, RR 0.19 95% CI 0.03-1.20).[3, 22] Similarly comparing RPCA to EA showed no significantly different risk of acidosis in the neonates (5 studies; RPCA 933, EA 950 women, RR 0.75 95% CI 0.45-1.25).[10, 13, 20, 23, 25]

Naloxone. Nine studies, including 2944 women, reported the neonatal need for naloxone. Four studies compared RPCA (120 women) to other opioids (171 women) with 3 out of 4 studies reporting the absence of need for naloxone.[3, 6, 22, 26] In only one study one neonate required naloxone in the pethidine group (RR 1.14 95% CI 0.88-1.49).[6] Five studies compared RPCA (1143 women) to epidural analgesia (1130 women) and reported zero use of naloxone.[10, 13, 20, 23, 24]

Discussion

Fourteen randomised controlled trials and 2 observational studies were included in this systematic review and meta-analysis evaluating safety and side effects of RPCA compared to other analgesic methods during labour. Our meta-analysis of 430 parturients showed no statistically significant different risk of low saturation levels (SpO_2 < 95%) in women receiving RPCA compared to other opioids. This result is supported by a previous analysis performed in 2011 comparing RPCA to pethidine, which did not find a significant difference in saturation levels between treatments.[4] In contrast, our analysis of 2,727 women showed that relative to EA, RPCA is associated with significantly more episodes with SpO_2 levels < 95%. Similar results were obtained for SpO_2 levels <90%. Regarding the incidences of low respiratory rates (<8) or hypotension there seemed to be no significant differences among treatments. However, our results are probably biased by the fact that these parameters were poorly reported. Since remifentanil is a potent opioid agonist, it is likely that it has sedative effects in parturients. Compared to other opioids the level of sedation was comparable. Compared to EA, 4 out of 6 studies found significantly more sedation during administration of RPCA. Our analyses together with the five published case reports describing serious (cardio)respiratory events during administration of remifentanil,[14-18] justifies the statement that treatment of labour pain with RPCA is associated with a serious risk for developing serious respiratory depression. We and others therefore strongly recommend that all parturients treated with RPCA are closely and continuously monitored, for example by continuous pulse oximetry or respiratory rate monitoring.[4, 27-30]

In terms of risk of a caesarean section no significant difference was observed among treatments. This is in agreement with previous systematic reviews comparing various methods of pain relief during labour.[31, 32] Interestingly, the need for instrumental delivery was not significantly different among treatments. This stands in contrast to the results of a systematic review from 2012, comparing EA against non-EA methods, which showed that women using EA were at increased risk of an instrumental delivery.[31]

Our systematic review did not show any significant differences regarding to fetal heart rate traces or neonatal scores including Apgar scores and umbilical pH. None of the included trials described any neonatal adverse outcomes caused by remifentanil.

Limitations

There are some limitations to our review. First, there is substantial heterogeneity between studies with respect to various dose regimens, different pump settings and different comparative drugs regimens. In some studies patient-controlled systems were compared to non-patient controlled (intramuscular or intravenous injections). Moreover, several studies allowed the use of N_2O (Entonox), which may have affected results. Secondly, included studies are relatively small and are mainly efficacy trials, not powered for a risk analysis of side effects. Different to previous systematic

reviews, we have also included observational studies, given the fact that these studies can be an important source of data for adverse effects.[33] A final consideration is the fact that different cut-off points for outcome measurements were taken; for example the duration of oxygen desaturation. The cut-off point for oxygen desaturation ranged from 20 seconds to 60 seconds in various studies. Moreover, some of the studies did not mention the cut-off point. These limitations have to be taken into account while interpreting the results from this review.

Conclusions

Implications for practice. RPCA during labour is associated with increased episodes of low oxygen saturation (< 95%). Compared to other opioids administered during labour no significant differences were found. Other side effects were comparable to other opioids during labour. With EA less desaturation, sedation and nausea was seen, but the technique is more invasive and sometimes contraindicated. With the available data, we conclude that remifentanil is a viable option for labour analgesia but because of safety concerns with respect to respiratory depression careful monitoring and close observation are required.

Implications for research. Several efficacy trials reported side effects as secondary outcome measurements, however data on safety issues remain limited. Only one study reported an adverse event. More large case series reporting on safety or randomised trials comparing side effects are needed to make a more accurate risk-to-benefit analysis.

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8

A retrospective study on persistent pain after childbirth in the Netherlands

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Abstract

Reported prevalence rates of persistent postpartum pain (PPP) range from less than 1% to almost 20%. The aim of this study was to examine the prevalence of PPP in a Dutch cohort and to evaluate a possible causal role for specific risk factors on the development of chronic pain after childbirth. A questionnaire was sent to 960 postpartum women approximately 2 years after delivery. Primary outcome was pain that arose from childbirth at follow-up, and secondary outcomes included quality of life (QoL) and Hospital Anxiety and Depression Scale scores. Tested risk factors included mode of labor analgesia, history of negative effect, history of chronic pain, delivery route, parity, and ethnicity. A total of 495 (51.6%) women participated. At a mean time of 2.3 postpartum years, 7.3% of women reported any pain and 6.1% reported significant pain related to the delivery. Compared to spontaneous delivery, cesarean delivery provided protection against persistent pain (odds ratio, 0.12; 95% CI, 0.01–0.63, P<0.05). None of the other risk factors, including remifentanil use for labor pain, were of influence on the prevalence of persistent pain. Women with PPP experienced greater negative effects and had lower QoL scores compared to women without pain. In this cohort of Dutch patients, PPP is a serious problem with a great impact on the physical and mental health of women.

Introduction

Both vaginal and cesarean delivery are associated with significant tissue damage. Vaginal deliveries are associated with uterine contractions, dilation of the cervix and lower uterine segment, stretching and compression of pelvic and perineal structures, inflammation of cervical tissue, and tears in the birth canal.[1,2] During a cesarean section (CS), tissue damage is related to the skin incision, traction on abdominal muscles and nerves, and incision in the lower segment of the uterus.[2] Multiple studies show that severe pain following surgery is linked to development of chronic or persistent pain.[3,4] Pain following childbirth is not different in this respect. The reported prevalence of persistent postpartum pain (PPP) in women who gave birth either vaginally or by CS varies from less than 1% to almost 20%.[1,2,5–9] Apart from the differences in study samples and methods to report pain, this large range might be explained by the fact that most previous studies did not discriminate between preexisting and new onset pain from delivery.[5,7,9] In contrast, Eisenach et al[2] defined the primary outcome measure as pain which began during delivery at a location which could be attributed to the delivery (eg, pelvis, perineum, and abdomen). In their study, PPP after childbirth was relatively rare, with a prevalence of 1.8% at 6 months and 0.3% at 12 months.

In this study, we examined the prevalence of PPP in a cohort of Dutch women. We surveyed women who had participated in the RAVEL (Remifentanil patient controlled analgesia versus epidural analgesia during labor) trial.[10] This multicenter randomized controlled equivalence trial examined the effect of remifentanil patient-controlled analgesia (RPCA) vs epidural analgesia (EA) for labor pain. Approximately 2 years after delivery, the women were queried about the presence of PPP as well as for signs of anxiety and depression. Additionally, the women were asked to recollect pain at 3 months after childbirth (the end of maternity leave in the Netherlands) and at the first birthday of the child to get an impression of the course of PPP. Logistic regression models were constructed to estimate the role of specific risk factors in the development of PPP. An important risk factor for development of postoperative persistent pain is treatment with remifentanil during surgery[11,12] Extrapolating these data to the perinatal setting leads to the hypothesis that the use of RPCA for labor pain may be associated with more complaints of PPP following childbirth compared to no analgesic treatment or epidural labor analgesia.

Methods

Study design and population

The RAVEL trial was registered in the Dutch Trial Register (http://www.trialregister.nl) under number NTR2551. Women who had participated in that trial received a follow-up questionnaire in July 2014.[10] In that trial, 1,414 parturients who received secondary or tertiary obstetric care (obstetric care at home was excluded) in one of 15 participating hospitals in the Netherlands were randomized to RPCA (30 µg bolus with a lockout time of 3 minutes) or EA (either with ropivacaine/ sufentanil, bupivacaine/sufentanil, levobupivacaine/sufentanil, or bupivacaine/fentanyl), should they ask for

pain relief during labor. The inclusion criteria for this follow-up study were participation in the RAVEL trial, age ≥18 years, and American Society of Anesthesiologists (ASA) physical status I or II. Women were excluded for follow-up if the written informed consent form was not present, if there was no permission to be contacted for follow-up study, if no contact information was available, or if the child had died. Women who delivered by primary CS were excluded in the analysis of the RAVEL trial, and therefore no data were available for this follow-up study. The study protocol was approved by the Leiden University Medical Center medical ethics committee.

Data collections and outcome measures

Women received an e-mail link to the Dutch Postpartum Chronic Pain Questionnaire (DPCPQ) or a paper version. The questionnaire was designed to assess pain complaints that began during delivery and were still present at three specific times after childbirth: end of maternity leave, first birthday of the child, and time of the survey. The DPCPQ was made up of questions from specific surveys including the McGill Pain Questionnaire and the Hospital Anxiety and Depression Score (HADS),[13,14] as well as additional questions aimed at the presence of pain before and during pregnancy and the quality of life (QoL). The English translation of the DPCPQ is available from the authors. Since we had access to the database of the RAVEL trial, specific data regarding baseline patient and delivery characteristics were taken from the original RAVEL database. The following items were collected: pain at three postpartum time points, labor analgesia (RPCA, EA, or no analgesia), delivery route (spontaneous vaginal, instrumental vaginal, or CS), maternal age at delivery, body mass index (obtained at 3 months of pregnancy), ethnicity, ASA class, history of chronic pain, history of abdominal or back surgery, history of depression and mood disorders, parity, multiple pregnancy, the health-related QoL at the time of the survey (scored on a 10-point scale; question 18 of the DPCPQ), and anxiety and depression score at the time of the survey (derived from the HADS questionnaire). The HADS scores were divided into three subgroups: 0–7, 8–10, and 11–21 points, indicating absence, possible, and probable presence of anxiety or depression, respectively.

The primary outcome measures were 1) pain, defined as pain scored on an 11-point numerical rating scale (NRS) with a score ≥1, which was present at the time of the survey and strictly localized at the lower back, abdomen, pelvis, vagina, or perianal area, and which began during delivery, and 2) significant pain, defined as pain as described above but with an NRS ≥3 and/or which interfered with normal daily activities, including child care, housekeeping, or work. Secondary outcome measures were the health-related QoL, anxiety, and depression scores at the time of the survey.

Statistical analysis

Multivariate logistic regression was used to estimate the odds ratio (OR) for the occurrence of pain and significant pain at the time of the survey, adjusting for risk factors. To identify potential risk factors, univariate logistic regression models were fit to the data. Initial risk factors tested were type of labor analgesia, conversion from EA to RPCA or from RPCA to EA, history of depression and anxiety, history of chronic pain, history of back or abdominal surgery, delivery route, parity, and

ethnicity. Those factors with a Wald test P-value of <0.20 were taken into the multivariable model. Two separate logistic models were constructed. The first was on the total population, and the second was on the women who received either EA or RPCA. For secondary endpoints, differences in the QoL and HADS scores between patients without and with significant pain were assessed using t-tests. The HADS score before childbirth was compared to the recent score with a paired sample t-test. SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. P-values ≤0.05 were considered significant.

Results

Of the 1,414 women enrolled in the RAVEL trial, 960 women did not object to participate in follow-up studies (Figure 1).

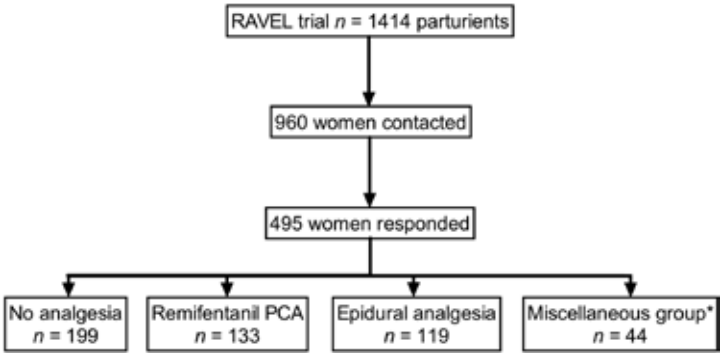

Figure 1. Flow chart of the study.
Note: *This group includes women who received intramuscular morphine for labor analgesia, delivered by elective primary cesarean section, or received both types of analgesia consecutively during labor.

The response rate was 51.6% (n=495; last questionnaire received August 18, 2014). Of these 495 women, 346 had a spontaneous vaginal delivery, 42 an instrumental vaginal delivery, 95 a (secondary) CS, and there were 12 missing values. The number of women treated with RPCA and EA for labor pain was 133 and 119, respectively; 199 women received no pain relief. The remaining 44 women received intramuscular morphine, delivered by elective primary CS, or received both types of analgesia consecutively during labor. Table 1 gives the baseline characteristics of the parturients. In the group of women who did not receive analgesia, there were significantly more multiparous women (P<0.001) and less women with a multiple pregnancy (P=0.04) compared to the women who did receive analgesia. Other items did not differ between treatment groups.

Table 1. Baseline characteristics of the participating women

		Mode of labor analgesia		
	Complete set *n* **= 495**	**None** *n* **= 199**	**Remifentanil PCA** *n* **= 133**	**Epidural Analgesia** *n* **= 119**
Maternal Age (years; mean ± SD) $	34.6 ± 4.5	34.6 ± 3.9	4.4 ± 5.0	34.8 ± 4.6
Ethnic Origin: Caucasian	426	167	124	112
≥ Higher education	251	96	65	73
BMI (kg/m²; mean ± SD) #	24.7 ± 4.3	24.4 ± 4.4	24.6 ± 4.3	25.3 ± 4.2
ASA classification				
1	328	128	98	87
2	144	70	35	31
Parity *				
0	244	77	70	75
≥ 1	228	121*	63	43
Multiple pregnancy	24	6*	7	10
Time to Follow Up (years; mean ± SD)	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3	2.3 ± 0.3

Data are *n* unless otherwise indicated; $ age at time of the delivery; # Body mass index (BMI) obtained at 3 months of pregnancy. * In the group of women who did not receive analgesia there were significant more multiparous women ($p < 0.001$) and less women with a multiple pregnancy ($p = 0.041$) compared to the women who did receive analgesia.

Prevalence of persistent pain following childbirth

The mean time interval from delivery to the survey was 2.3 (SD: 0.3; range: 1.3–3.2 years). In Figure 2, the occurrence of PPP is given for the total population and for the three distinct treatment groups. At the time of the survey, 7.3% (95% confidence interval [CI], 5.1%–9.9%; n=35) of women reported any pain (NRS >0). The median NRS was 4.5, with an interquartile range of 4.0. Pain frequency ranged from daily (n=9) to near-daily pain (2–31 days without pain in the preceding month). There was no difference in demographics between women who developed pain and those who did not. Pain complaints were chiefly localized to the lower abdomen, pelvis, lower back, tailbone, vagina, perianal area, and/or groin. Thirty of these women (6.1%, 4.1%–8.5%) indicated that the pain was significant with an NRS ≥3 and pain affecting their daily activities (eg, child care, housekeeping, and/ or work); 23 had visited a doctor because of the pain and 13 required analgesia. In eleven women, the pain was such that it affected their sleep pattern.

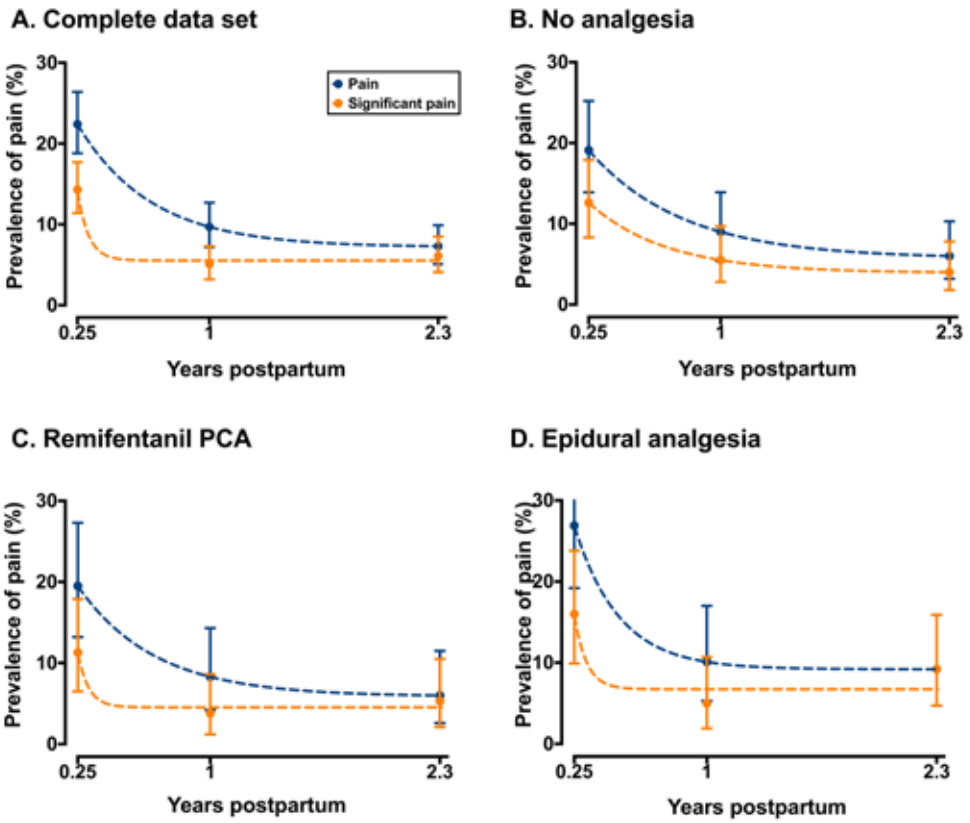

Figure 2. Pain that began during delivery and was located in the lower back, abdomen, pelvis, vagina, or perianal area reported at the time of the survey (on average 2.3 years following childbirth) and retrospectively at 3 months and 1 year following childbirth. Notes: The data are shown for the total population (A) and women who received no analgesia during labor (B), women who received remifentanil Pca during labor (C) and women who received epidural analgesia during labor (D). Data are mean ± upper and lower 95% confidence interval. Blue dots indicate all reported pain; orange dots indicate significant pain (NRS $3 and/or pain which interfered with childcare, housekeeping, or work). To guide the eye, exponential functions are fit through the data.

Approximately 111 women reported PPP at the end of the maternity leave (22.4%; 95% CI, 18.8%–26.4%); 71 (14.3%, 11.4%–17.7%) reported significant pain. Fortyeight women reported that they had PPP at the first birthday of their child (9.7%, 7.2%–12.7%); 25 (5.1%, 3.2%–7.3%) had significant pain.

Logistic regression analysis showed that various factors did not reach the cutoff level of P<0.02 in the univariate analysis, including history of depression and anxiety (negative effect), history of chronic pain, and history of back or abdominal surgery. The results of the analysis on the multivariate analysis of the complete data set are given in Table 2. Compared to women with no request for analgesia during labor, neither RPCA nor EA was a significant risk factor for PPP or significant PPP. Similarly, factor conversion, ethnicity, parity, and assisted vaginal delivery did not have influence on the prevalence of PPP. Women who delivered via CS were protected for development of PPP (one of 95 women; OR: 0.13, 95% CI: 0.01–0.64, P<0.05) and significant PPP (one of 95 women;

OR: 0.12, 95% CI: 0.01–0.63, P<0.05) relative to women who spontaneously delivered (29 and 23 of 346 women had pain and significant pain, respectively). There was no added pain prevalence in women exposed to remifentanil during labor compared to women who received EA, with an OR of 1.95 (95% CI, 0.71–5.30; P>0.05) for pain and 0.45 (95% CI, 0.16–1.27, P.0>05) for significant pain.

QoI, anxiety, and depression following childbirth

At an average of 2.3 years following childbirth, women with pain had a lower QoL score than women without pain: 7.0 [1.1] vs 7.8 [1.1], respectively (P<0.001).

Mean anxiety scores in women with and without significant pain were 6.6 [4.1] and 4.6 [3.1] (P=0.008), respectively. Approximately 19.4% (95% CI, 8.2%–36.0%, n=7) of women with PPP had probable anxiety (HADS score 11–21) vs 5.1% (3.2%–7.5%, n=23) of women without pain. Approximately 27.7% (14.2%–45.2%, n=10) of women with PPP had possible (score 7–10) or probable anxiety vs 16.5% (13.2%–20.3%, n=75) of women without pain (Figure 3).

Mean depression scores in women with and without significant PPP were 4.6±3.8 and 2.6±2.8 (P=0.004), respectively.

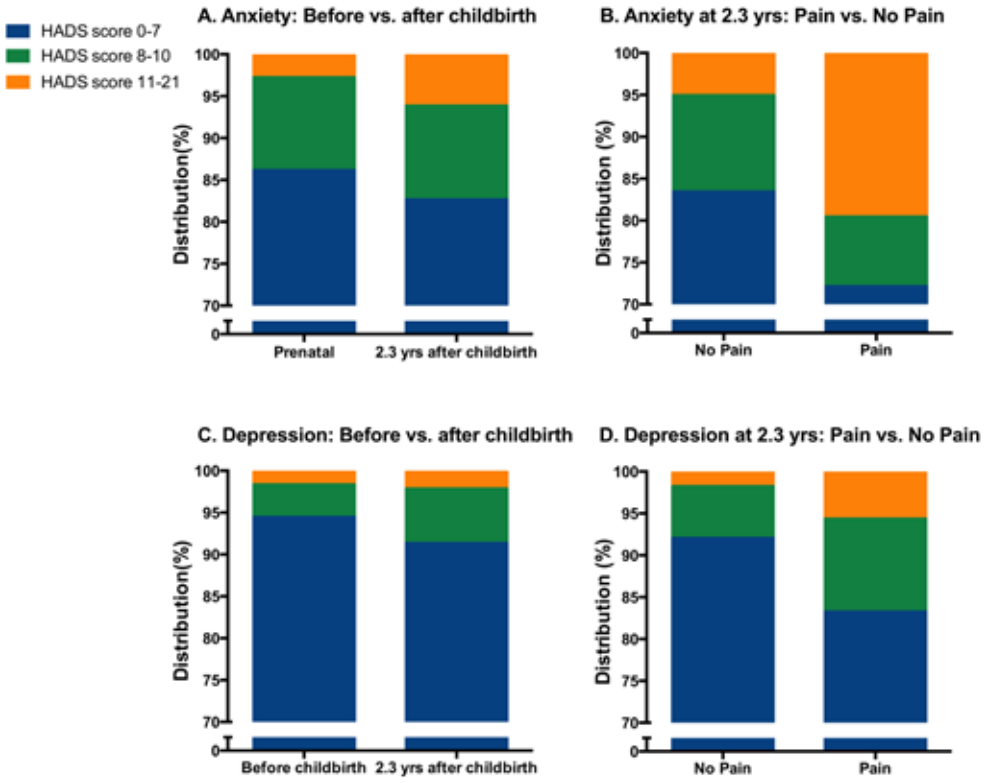

Figure 3. Distribution of HADS scores for anxiety and depression.

Notes: (A) anxiety scores: before delivery vs on average 2.3 years after delivery. (B) anxiety scores in women without vs with pain. (C) Depression scores: before vs on average 2.3 years after delivery. (D) Depression scores in women without vs with pain. haDs scores 0–7, 8–10, and 11–21 points indicate absence, possible, and probable presence of anxiety or depression, respectively.

Approximately 5.6% (95% CI, 0.7%–18.7%, n=2) of women with PPP had probable depression (HADS score 11–21) vs 1.8% (0.8%–3.4%, n=8) of women without pain; 16.7% (6.4%–32.8%, n=6) of women with PPP had possible (score 7–10) or probable depression vs 7.9% (5.6%–10.8%, n=36) without pain (Figure 3).

There were no differences in prenatal HADS scores between women who would develop PPP and who would not, with mean scores for anxiety 4.9 [2.4] (significant pain) and 4.5 [2.9] (no pain, P=0.516) and mean scores for depression 3.5 [2.8] (significant pain) and 2.7 [2.5] (no pain, P=0.116), respectively (Figure 3).

Discussion

Taken the many millions of births each year, the occurrence of PPP that interferes with the daily activities in even a small percentage of women will have a large socioeconomic impact. In our cohort of 495 Dutch women, significant pain attributed to the delivery process was present in 6.1% (any pain in 7.3%) of women, on average 2.3 years after childbirth. Extrapolation of these findings to the 170,000 deliveries per year in the Netherlands suggests that approximately 10,000 women are affected yearly with significant pain.[15] The presence of persistent pain was associated with a reduced health-related QoL and a fourfold higher prevalence of anxiety symptoms and threefold higher prevalence of negative-effect-related symptoms compared to women without pain. A protective effect was observed following CS, while none of the other risk factors influenced the prevalence of PPP. Importantly, treatment of labor pain with either EA or RPCA had no effect on the occurrence of pain. Retrospective questions in our survey revealed that the prevalence of significant pain at the end of maternity leave was 14.3% (any pain 22.4%) and at the child's first birthday was 5.1% (any pain 9.7%), which indicates that no resolution occurred in the second year of postpartum pain.

The questions in the DPCPQ were such that the women were forced to restrict pain reporting to symptoms that arose during delivery (ie, "new" pain). The 95% lower limit of significant pain prevalence at the time of the survey was 4.1%. The response rate of our survey (~52%) was relatively low and may have caused an outcome bias. One possibility is that the women who did not respond were without any pain complaints at the time of the survey. Taking this assumption into account, the prevalence of significant pain might be as low as 3.1% with a lower limit of 2.1%. This is still considerably higher than the recently reported prevalence rate in the study by Eisenach et al,[2] who showed that women in the United States have a PPP prevalence of 0.3% at 1-year postdelivery. As indicated previously, Eisenach et al[2] also restricted the analysis to "new" pain. Apart from the evident differences in protocols (the US study was a prospective longitudinal cohort trial in two tertiary centers in North Carolina and New York), specific circumstances surrounding the delivery process may differ. Eisenach et al[6] showed further that the severity of acute pain after delivery was associated with the risk of transition to chronic pain. This would suggest that women in the Dutch cohort experienced more severe acute pain after delivery than women in the USA. We

did not query the women regarding immediate postpartum pain. The first interaction of the mother with her newborn child is highly emotional and we contend that this may have affected the mothers' recollection at that moment in time. Still, there are no reasons to assume any differences in intra- and postpartum care between the two countries, and hence, any difference in acute postpartum pain between studies. Another possibility for the difference in outcome may be related to the number of CSs. The number of CSs was greater in the US cohort (32% vs 19%).[2] Still in the US study, the mode of delivery did not represent a significant risk factor for chronic pain development, and in our study women who delivered predominantly by secondary CS were relatively protected from PPP development. Alternatively, and possibly most importantly, there may be biopsychosocial differences surrounding delivery that may play a causal role in the difference in PPP development between the two cohorts (eg, factors related to endogenous modulation of pain, pain catastrophizing, coping strategies, genetics, etc). Future prospective studies should address which risk factors for chronic pain are responsible for the relatively high PPP rates observed in the Netherlands.

The survey was taken on average 2.3 years after delivery. Since the RAVEL trial was not designed to study PPP, we had to rely on retrospective questions to assess pain complaints at 3 months and 1 year after childbirth, introducing a possible recall bias. It is likely that women who experienced pain at the time that they received the DPCPQ read and pondered the retrospective questions more thoroughly than the women without pain. However, by focusing on two time points, which most probably had a rather large impact on the women's life (end of maternity leave and first birthday of the child), we believe that we created two windows of increased awareness regarding possible pain symptoms. Consequently, we contend that this may have increased the reliability of answers, also in women without pain at the time of the survey. We relate the small increase in significant pain from 1 to on average 2.3 years after delivery (from 5.1% to 6.1%, Figure 2A), apart from the obvious recall bias, to the possibility that chronic pain is not a continuous symptom but fluctuates over time in terms of severity. These data suggest that chronic postpartum pain resolution more than 1 year following childbirth is tedious. In future surveys, we will further monitor the course of pain in our cohort.

We had to reject our hypothesis that, in common with intraoperative use of remifentanil, obstetric RPCA increases the prevalence of PPP. Although we corrected for possible confounders, the study may have been underpowered to detect a remifentanil effect. Another explanation may be that the remifentanil dose is an important factor in the development of chronic pain. The mean remifentanil dose in our study was 1.49 mg; much higher doses are given during anesthesia. This reasoning is supported by the reported dose-dependent impact of remifentanil analgesia on the development of chronic thoracic pain after sternotomy.[12]

Somewhat unexpectedly, CS protected the women from PPP compared to spontaneous vaginal delivery, with just one woman (out of 95) with PPP following CS (OR 0.12 for pain and 0.13 for significant pain, Table 1). In most women, CS was performed under spinal or epidural anesthesia. For postoperative analgesia, paracetamol, opioids (eg, methadone or morphine), and nonsteroidal anti-inflammatory drugs were given in case of CS. As discussed by Eisenach et al,2 it is reasonable to assume that tissue injuries during surgery for a CS, such as traction on abdominal structures and

nerves (eg, the ilio-inguinal and hypogastric nerves) and damage to the lower uterine segment, would increase the likelihood of PPP. In our cohort, most women who delivered by CS had contractions and some degree of cervical dilation (secondary CS occurred in 84 of 95 women), adding to the degree of tissue injury that could cause persistent pain. It is plausible that the protective effect of CS is related to the postoperative treatment of pain with opioid and/or EA. This reasoning is in agreement with the theory that severe postpartum pain is associated with a high probability of development of PPP,[3] and suggests that effective relief of severe pain after vaginal delivery, for example by EA, would reduce the prevalence of PPP.[1]

We established once more that PPP and negative effect are comorbid.[16] While prenatal anxiety and depression scores were not different between women who developed PPP and those who did not, at the time of the survey the differences in HADS were significant with greater anxiety and depression scores and a reduced QoL in women with PPP compared to those without pain (Figure 3). This exemplifies the impact of chronic pain on the mental health of this relatively young population. Interestingly, we did not find a correlation between negative effect before delivery and the development of PPP. While for the transition from acute postsurgical pain to persistent pain this correlation is well established,[17–19] this association is less apparent for PPP.[2,7]

The patient population that was targeted in our study included women in secondary and tertiary obstetric care. Since more than 20% of pregnant women in the Netherlands give birth in primary, midwife-led care, our results do not apply to the total population of Dutch pregnant women. Development of chronic pain in primary obstetric care remains unknown at present. Other limitations of the study included the relatively low response rate (52%) and the retrospective nature of our study. Our study differs from most previous studies in that it, in contrast to our current study, did not make a distinction between pain complaints specifically related to childbirth and preexistent pain. Taken together, we contend that despite some limitations our study shows that persistent significant “new” pain following childbirth in this Dutch cohort is a serious problem with a relatively high prevalence at 2 years postpartum.

Conclusion

We retrospectively surveyed women on the prevalence of persistent pain following childbirth that began during delivery. We observed that in 495 women, at a mean time of 2.3 postpartum years, 6.1% complained of significant pain related to delivery. Compared to spontaneous delivery, cesarean delivery provided protection against persistent pain. Our results further show important implications for the physical and mental health of the women in pain.

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9

General discussion

In this thesis I present the results of the analysis of the primary outcomes (satisfaction with analgesia and costs) of the RAVEL trial and of sub analyses addressing secondary outcomes regarding safety. The RAVEL trial compared the use of remifentanil PCA to epidural analgesia as analgesia during labour.

We found that women randomised to epidural analgesia were more satisfied with their pain relief than women randomised to remifentanil PCA. There was no difference in costs between both strategies. With respect to safety, remifentanil PCA increases the risk of maternal desaturation as was shown in the RAVEL cohort as well as in meta-analysis of previously published studies. Pain relief during labour with remifentanil does not appear to increase the risk of persistent postpartum pain.

In this final chapter I will first discuss our findings in relation to the results of previous studies and discuss the strengths and weaknesses of our study. I will finish with questions that remain after previous described findings and give directions for future research and focus on implications for clinical care.

Effectiveness of remifentanil PCA and satisfaction with pain relief

Superiority of epidural analgesia to remifentanil PCA in improving pain intensity scores was established in the first trials comparing these types of analgesia but equality in satisfaction with pain relief was suspected.[1,2] These studies, however, were powered to detect a difference in pain intensity scores not a difference in satisfaction. The RAVEL trial showed that remifentanil PCA is inferior to epidural analgesia with respect to satisfaction with pain relief. Our findings regarding pain intensity were comparable to previous published studies showing significantly lower pain intensity scores in the epidural group. Since our study was designed to prove equality in satisfaction with analgesia between both strategies there was sufficient power to reject equality.

Our subgroup analysis shows that epidural analgesia is superior to remifentanil PCA with respect to pain intensity and satisfaction in all subgroups including multiparous women. However, theoretically a group of women might benefit from having access to remifentanil PCA as an alternative to epidural analgesia. These are the women that deliver quickly after the request for analgesia, they can be multiparous women or nulliparous women in the last part of the first stage of labour. In the following paragraph I will discuss this matter.

Subgroup analysis in our study of only *multiparous* women showed that this subgroup is more satisfied with epidural analgesia than with remifentanil PCA. Logtenberg et al performed a randomised controlled trial of remifentanil PCA and epidural analgesia with the same study design as the RAVEL trial in women of low obstetric risk.[3] Their results were the same as the RAVEL trial with respect to pain intensity scores and satisfaction. They found no significant difference in satisfaction with analgesia in their subgroup analysis of multiparous women. In their study, women were more likely not to receive any analgesia despite of their request when randomised to epidural analgesia. In the remifentanil allocated group 10% did not receive analgesia compared to 25%

in the epidural allocated group. This could be due to anaesthesiologists being reluctant to start epidural analgesia when rapid progression to the second stage of labour is expected or because these women delivered before the epidural catheter could be placed. We hypothesize that this subgroup of women (i.e. multiparous women) with a request for pain relief might benefit from having access to alternatives to epidural analgesia such as remifentanil PCA which are possibly quicker and easier to start. Further research on satisfaction with analgesia in multiparous women at all stages of labour is needed.

Women *delivering within a relative short time* after a request for analgesia might benefit from having access to alternative pain relief other than epidural analgesia. An RCT comparing remifentanil PCA to fentanyl and meperidine PCA showed that remifentanil PCA provide better reduction of pain intensity scores than controls but that pain scores return to baseline after four hours.[4] With these data Douma et al. concluded that remifentanil PCA should be considered only when delivery is expected within this time frame. Considering these results a subgroup of women that could benefit from alternatives to epidural analgesia are parturients who request analgesia late in the first stage of labour, when a quick delivery is expected.

Future studies with adequate power are needed to make a good assessment if these women that are expected to deliver within a relative short time after a request for analgesia, could benefit from alternative methods of analgesia like remifentanil. Until these studies are performed the results of our study demonstrate that epidural analgesia is superior to remifentanil PCA in terms of efficacy and satisfaction.

Costs of remifentanil PCA and epidural analgesia

One previous trial and one review report on the costs of epidural analgesia versus intravenous analgesia.[5,6] In general costs of labour analgesia consists of two components, first baseline costs for labour which are equal in both groups and second incremental costs associated with complications and involvement of anaesthesiological nursing and staff. In both the study of Macario and our study cost effectiveness analysis was not performed because direct or indirect benefits for society are largely intangible. The incremental costs for analgesia of epidural analgesia were estimated by Macario et al. at $338, largely because of the increase in costs due to involvement of an anaesthesiologist.

Our trial was, to our knowledge, the first trial addressing costs of remifentanil PCA and epidural analgesia. From an economic perspective, there is no preferential pain treatment in labouring women. Though not statistically significant, remifentanil PCA would appear to be less expensive than epidural analgesia. The difference in total costs from the start of labour until ten days post-partum is -282 euro, the difference in costs of analgesia only is -2 euro. The main difference is due to a difference in costs for neonatal admission and since there is no difference in the percentage of neonates admitted or the reasons for admission between groups we have to assume this difference is based on chance. When developing the study protocol and calculating a possible difference in costs we thought that remifentanil PCA would be administered without the intervention of an anaesthesiologist, thus making it the less expensive alternative due to lower personnel costs. Our

economic evaluation proved otherwise, there is no significant difference in costs between both strategies.

Safety of remifentanil PCA as labour analgesic

The major concern with remifentanil are respiratory complications which could be life threatening to both mother and fetus. Previous studies show lower saturation scores and more episodes of desaturation in women using remifentanil PCA compared to epidural analgesia. Our meta-analysis (chapter 7) confirms the findings on maternal respiratory complications reported previously. We included 14 RCTs and 2 observational studies. Compared to other opioids there was no significant difference in maternal desaturation (SpO2 <95%) in women treated with remifentanil PCA. However, five studies did report a higher incidence of desaturation, so a distinct trend towards more desaturation was observed. Compared to epidural analgesia women using remifentanil PCA had significantly more desaturation (SpO2 <90% and <95%). The incidence of low respiratory rate (<8) was poorly reported but no significant difference was found.

Five case-reports have been published on serious complications in women using remifentanil during labour, three describe a respiratory arrest and two a cardio-respiratory arrest. Of the cases of respiratory depression one occurred in a woman treated with only continuous infusion (rate 0.1 µg-kg-min),[7] one in a woman that had previously had epidural analgesia so an opioid overdose was suspected[8] and one in a woman treated with 40 µg boluses with a lockout of 2 minutes[9]. Of the cases of cardio-respiratory arrest one woman received a bolus dose of 400 µg due to a mistake in the preparation of the medication[10] and the other received remifentanil after also receiving codeine and diamorphine so in this case an opioid overdose was also suspected.[11] All authors judge that maternal monitoring, especially monitoring saturation and one-to-one nursing is vital and that this one-to-one nursing entails that a nurse trained in basic life support and mask ventilation should be present in the labour room at all times.

Safety of women using remifentanil PCA as labour analgesia is only guaranteed with strict monitoring and safety measures. As desaturation is a late sign of respiratory depression one-to-one nursing or capnography are the only methods to detect respiratory depression when it occurs. Because it was unclear how labouring women on remifentanil in Dutch hospitals were monitored, the Dutch Health Inspectorate (Inspectie voor de Gezondheidszorg: IGZ) ordered the Societies of Gynaecologists (NVOG), Anaesthesiologists (NVA), Midwives (KNOV) and clinical Pharmacologists (NVZA) in 2013 to develop a guideline[12] for the use of remifentanil PCA on the labour ward after learning that remifentanil was used outside of clinical trials in numerous Dutch hospitals. It is important that women are monitored by a health care professional that is trained in basic life support as the most important side effect of a potent opioid like remifentanil is respiratory depression. An anaesthesiologist, obstetrician or clinical midwife should be present in the labour room during the first 30 minutes after the start of remifentanil and after every increase in bolus dose. A nurse should be present for the minimum of the first hour but continuous one-to-one nursing is advised.[12] Because our study (chapter 6) showed that oxygen saturation is significantly lower at all times we argue that one-to-one nursing should be mandatory when using remifentanil for labour analgesia.

It is unclear at this moment to what extend these recommendations are implemented in Dutch hospitals. Only hospitals that comply with these recommendations will have a safe infrastructure for the administration of remifentanil on the labour ward. In future perspectives we will propose ways to evaluate compliance with guidelines and registration of side-effects and adverse events.

Analysis of maternal parameters from the RAVEL trial showed that maternal temperature was significantly higher in women in the epidural analgesia group, with a higher incidence of fever (temperature >38 °C), and that this persisted throughout labour. Also, more women were treated with antibiotics for suspicion of intrauterine infection. Our findings are in agreement with the results of previous studies.[7,13-17] Our meta-analysis did not find a difference in rates of caesarean section nor vaginal instrumental delivery. This in contrast to the results of an earlier meta-analysis[18] which showed an increased risk of vaginal instrumental delivery in women using epidural analgesia.

Concerns have been raised about long term consequences on intrapartum use of opioids and neurodevelopmental issues in childhood and a higher risk of substance abuse in adulthood. No long term follow up studies on opioids during labour have been performed to our knowledge. However, there are a few studies that address the effects of opioid use during labour in human and animal studies and follow up of children that received opioids in the NICU. Neonatal depression after opioids exposure in utero can last up to three days.[19] Animal studies suggest that the use of opioids in infants might have an increased risk of hypersensitivity, impaired learning and neurobehavioral deficits in childhood.[20] Follow up of neonates treated with morphine when admitted at a NICU at five and nine years of age shows no negative consequences in terms of intelligence, visual motor integration and behaviour.[20]

The reported prevalence of persistent postpartum pain (PPP) in women who gave birth either vaginally or by CS in previous studies varies from less than 1% to almost 20%.[21-29] Apart from the differences in study samples and methods to report pain, this large range might be explained by the fact that most studies did not discriminate between pre-existing and new onset pain from delivery and did not specify the location of this chronic pain.[24,26,28] In contrast, Eisenach et al defined the primary outcome measure as pain which began during delivery at a location which could be attributed to the delivery (e.g., pelvis, perineum, and abdomen). In their study, PPP after childbirth was relatively rare, with a prevalence of 1.8% at 6 months and 0.3% at 12 months.[22] Their study and definition of PPP is similar to the one we used for our study. In our cohort 7.3% of women reported any pain and 6.1% reported significant pain related to the delivery. Compared to spontaneous delivery, caesarean delivery provided protection against persistent pain (odds ratio, 0.12; 95% CI, 0.01–0.63, P<0.05). It is plausible that the protective effect of caesarean section is related to the postoperative treatment of pain with opioid and/or epidural analgesia. This reasoning is in agreement with the theory that severe postpartum pain is associated with a high probability of development of PPP,[28] and suggests that effective relief of severe pain after vaginal delivery would reduce the prevalence of PPP.[21]

Future perspectives/Implications for future research

It is still unclear which women could potentially benefit from having access to remifentanil PCA as analgesia during labour. In my opinion, only women with a contra-indication for epidural analgesia or women where placement of the epidural catheter failed should be eligible to receive remifentanil PCA at this moment.

However, as described previously, there might be women that could benefit from remifentanil PCA. First, women that are expected to deliver quickly after their request for analgesia. Future research in multiparous women and women in the final stages of labour might define more indications for the use of remifentanil as pain relief in labour.

Second, as feeling in control and informed consent are important aspects of satisfaction with childbirth one could argue that women who are counselled appropriately on effectiveness (i.e. inferior to epidural analgesia), satisfaction and side-effects, should be able to have access to remifentanil PCA, provided that appropriate measures are taken to ensure safety of both mother and fetus.

Remifentanil is a potent opioid with a serious risk of causing respiratory problems. With the right monitoring and precautions remifentanil is a viable option for labour analgesia but at this moment it is unclear whether monitoring is performed according to the recommendations in the SOP. This has to be evaluated in the near future. It is important to know which hospitals use remifentanil as analgesia during labour, which women are eligible to receive remifentanil and how they are monitored. At the time of the writing of this discussion the IGZ is evaluating the use of remifentanil and monitoring by visiting random hospitals and inspecting their infrastructure and training. We have to develop an infrastructure for continuous registration and evaluation in the future. There should be a central organ to report adverse events, respiratory depression requiring ventilation and cardiac arrest. This can be one of the Colleges (e.g. working party on maternal morbidity (INOSS/NethOSS)) or the IGZ. The IGZ describes a calamity as an unexpected or unintended event that has a possible relation to quality of care and has serious consequences for the patient or results in permanent injury or death. Since this is already the way of reporting calamities it might be sensible to use this infrastructure for the monitoring of adverse events with remifentanil.

After ensuring safe monitoring of women that are treated with remifentanil we could evaluate if this has any effect on the incidence of serious adverse events with the side note that that incidence is currently unknown. Prospective case series are the best way to assess the incidence of side effects, but because serious adverse events (respiratory arrest, cardiac arrest) are rare very large numbers are required. In absence of large enough prospective trials more large case series are needed reporting on safety to make a more accurate risk-to-benefit analysis.

Several dose finding studies have been done, most using a flexible weight-dependent dose with or without the use of background infusion.[16,30,31] Hill et al recommend to use a dose of 40 μg with a lockout time of 2 minutes after reviewing all available data and weighing safety against efficacy. Because of an increase of respiratory complications they advise against the use of a background infusion.[32] There are no studies comparing this dose to different doses and no studies on optimal lockout time. This might be a subject for future research. An RCT comparing 30 to 40 μg or 30 to a

weight dependent dose and after the optimal dose is established comparing a lockout time of two minutes to three minutes might answer remaining questions.

This thesis focusses on remifentanil versus epidural analgesia and shows that remifentanil is inferior to epidural analgesia with respect to efficacy and satisfaction. The study performed by Douma el al concluded that remifentanil PCA gives better analgesia than fentanyl or meperidine PCA.[2] From this one might conclude that remifentanil might have a place between meperidine and epidural analgesia. Nitrous oxide is also used as labour analgesia, mostly by women in the final part of the first stage of labour. This is also the stage of labour where women might benefit most from remifentanil. To our knowledge one trial has been performed on efficacy of remifentanil and nitrous oxide. This was a double blind crossover trial in which remifentanil PCA and nitrous oxide were administered for 20 minutes each. Remifentanil provided better improvement of pain intensity scores and higher satisfaction. However, this was a small trial and possibly underpowered for satisfaction and both treatments were only given for twenty minutes.[33] An RCT on satisfaction of remifentanil PCA and nitrous oxide in the last phase of the first stage of labour could establish the position of remifentanil PCA and nitrous oxide as analgesia during labour.

Long term follow up until adulthood could assess the risk of addiction or substance abuse later in life in children of mothers who were treated with opioids during labour. No such follow up studies have been performed before. However, it is unclear whether such a study is feasible because of logistical problems with very long term follow up. Follow up for even shorter periods has been proven difficult because of relocation of patients and funding difficulties. The answers to these questions might come from the follow up of large cohorts, like the Generation R study[34] or similar future prospective cohort studies. This could help with the very large numbers needed for a not very common outcome.

In our study regarding chronic post-partum pain (PPP) we found a higher incidence of PPP than expected. This prompted the question of the prevalence of PPP in the Netherlands. We would like to study the prevalence of PPP in the Netherlands and possibly perform a prospective RCT on prophylactic analgesia in vaginal birth versus no prophylactic analgesia to test our hypothesis that the use of prophylactic analgesia explains the difference in chronic postpartum pain between women who underwent caesarean section and those who delivered vaginally.

Conclusion

Epidural analgesia provides superior analgesia to remifentanil PCA. Women randomised to epidural analgesia with a request for pain relief are more satisfied with their analgesia than women randomised to remifentanil PCA.

Costs of epidural analgesia and remifentanil PCA are not significantly different. From an economic perspective, there is no preferential pain treatment in labouring women.

Epidural analgesia is associated with a greater incidence of fever and significantly higher temperature. Remifentanil PCA has an effect on maternal SpO2 with significantly lower mean

SpO2 during the labour period. This shows that respiratory complications are a serious problem associated with remifentanil and that continuous monitoring by trained personnel is obligatory.
Persistent postpartum pain affects many women. Of surveyed women, 6.1% complained of significant pain related to delivery. Since this was a retrospective follow up study this results might be explained by the study design and these findings have to be evaluated by further research.

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10

Summary

This thesis describes the results of the RAVEL (remifentanil patient controlled analgesia versus epidural analgesia in labour) trial. The RAVEL trial was a randomised controlled equivalence trial (N=1358) comparing remifentanil patient controlled analgesia (PCA) and epidural analgesia as pain relief during labour. Because previous studies showed that, although epidural analgesia is superior to remifentanil PCA in terms of reduction of pain intensity scores, satisfaction with analgesia seemed to be comparable, we designed this trial as an equivalence trial to demonstrate equivalence in satisfaction with pain relief.

Chapter 1 is a general introduction where the most relevant literature and background information that form the basis of this thesis are provided.

Before start of the RAVEL trial we aimed to assess the use of remifentanil PCA and epidural analgesia in the Netherlands and to investigate beliefs of obstetricians and anaesthesiologists on analgesia through an online questionnaire. The Dutch guideline "Medicamenteuze pijnbestrijding tijdens de baring" advises to use remifentanil PCA only in clinical trials and to have epidural analgesia available for all women 24/7. As the use of remifentanil PCA is not recorded in the LVR (Landelijke Verloskundige Registratie) and it was not clear if epidural analgesia was available in all Dutch hospitals 24/7 a questionnaire seemed the right way to investigate these questions. The results of this questionnaire are presented in **chapter 2**. According to official LVR data 26.6% of women received some kind of medical pain relief during labour in 2010 (15% epidural analgesia, 11.6% opioids). 81% of respondents to the questionnaire stated that epidural analgesia was available to all women 24/7 on their request with 92% availability during all hours if there is a medical reason. Remifentanil PCA was used in 44% of teaching hospitals and 55% of district hospitals. The mean use of remifentanil PCA in hospitals that offered it was 23%. Comparing results of hospitals only offering epidural analgesia to hospitals offering both epidural analgesia and remifentanil PCA shows that in hospitals where only epidural analgesia was available the use of analgesia was 20% (8-43%) while in hospitals where both epidural analgesia and remifentanil PCA were available the use of analgesia was 38% (26-63%) ($p<0.001$).

Chapter 3 outlines the study protocol for the RAVEL trial as it was published before the start of the trial.

Chapter 4 describes the results of the primary research question on equivalence of patient satisfaction with remifentanil PCA compared to epidural analgesia. Satisfaction with pain was measured using a Visual Analogue Scale (VAS) throughout labour in all women and with these serial measurements an Area Under the Curve (AUC) was calculated. The AUC for pain appreciation during labour for all randomised women was lower in the remifentanil PCA group (difference -2.8, 95% CI -6.9 to 1.3). This does not exclude a potential clinically relevant difference; therefore we could not conclude that the treatments are equivalent. Furthermore, in the subgroup of women who did actually receive analgesia, the AUC for pain appreciation after start of pain relief was significantly lower in women with a request for pain relief randomised to remifentanil PCA (difference -10.4, 95% CI -13.9 to -7.0).

The same results were seen in the AUC for pain intensity scores; these were significantly higher in women randomised to remifentanil PCA. Women randomised to remifentanil PCA requested pain relief more often than women randomised to epidural analgesia (RR 1.3, 95% CI 1.2-1.5). Maternal and neonatal outcome we not significantly different in both groups. Some side effects were more often reported in women who did receive analgesia. Temperature was significantly higher and hypotension more frequent in the epidural analgesia group. Oxygen saturation was significantly lower with remifentanil PCA. There were four respiratory depressions reported of <8 breaths per minute in the remifentanil PCA group and none in the epidural group. Nausea was reported more frequent in the group randomised to remifentanil PCA, but vomiting and itching were not.

As our hypothesis was that remifentanil PCA would be equivalent to epidural analgesia with respect to patient satisfaction we planned to perform a cost effectiveness analysis. Because equivalence was not proven we performed a cost evaluation. **Chapter 5** presents these results. Mean costs for women randomised to remifentanil PCA were €2900 versus €3183 for women randomised to epidural analgesia (mean difference -€282 (95% CI -€611 to €47)). The largest part of this difference can be attributed to the higher costs of neonatal admission in the epidural group. This non-significant difference in costs for neonatal admission was -196 (95%CI -465 to 73). After the trial was finished a Standard Operating Procedure (SOP) for the use of remifentanil PCA on the labour ward was developed by the Dutch Heath Care Inspectorate (IGZ). So additionally we added scenario analysis post hoc to address the influence of the presence of an anaesthesiologist at the start of remifentanil PCA and to address the influence of continuous one to one nursing during administration of remifentanil. Taking only the costs of analgesia into account, the costs of remifentanil PCA increase when an anaesthesiologist is present at the start of analgesia and increase even more with continuous one to one nursing. Only when no anaesthesiologist is involved in the administration of remifentanil PCA and there is one to one nursing for only the first hour there is a significant difference in costs of analgesia in favour of remifentanil PCA.

In **chapter 6** we evaluate respiratory complications and temperature in women using remifentanil. In concurrence with other published data we showed that women experience more episodes of desaturation and have an overall lower mean SpO2 when using remifentanil. Epidural analgesia is associated with a greater incidence of fever and significantly higher temperature overall. Remifentanil PCA has an effect on maternal SpO2 with significantly lower mean SpO2 during the labour period. The effect on time course of saturation differs between remifentanil and epidural analgesia. We also saw more desaturation episodes <92% in the remifentanil group. This shows that respiratory complications are a serious problem associated with remifentanil and that continuous monitoring by trained personnel is advised.

After the publication of the RAVEL trial and the STER (Saturation and Temperature in Epidural analgesia and Remifentanil PCA) a meta-analysis of maternal parameters incorporating all published randomised controlled trials and observational studies that compared efficacy and side effects of

remifentanil with any other labour analgesic was performed. The results of this meta-analysis are presented in **chapter 7.** Overall, although results are not significant, a distinct trend towards more desaturation was seen during administration of remifentanil PCA compared to other opioids. There were significantly more episodes of desaturation (SpO2 <95%) during administration of remifentanil PCA compared to epidural analgesia. Furthermore, there was more sedation in remifentanil PCA compared to epidural analgesia, more pruritus in remifentanil compared to other opioids. There seemed to be no difference in low respiratory rate (<8) or hypotension, however these incidents are rare and were poorly reported. There was no difference in CTG tracings, neonatal scores and mode of delivery between groups. Close observation of parturients receiving remifentanil, particularly continuous oxygen saturation monitoring and the availability of oxygen is strongly recommended.

We retrospectively surveyed women on the prevalence of persistent pain following childbirth that began during delivery. The aim of this study was to examine the prevalence of persistent postpartum pain (PPP) in a Dutch cohort and to evaluate a possible causal role for specific risk factors and the use of analgesia on the development of chronic pain after childbirth. The results of this study are presented in **chapter 8**. We observed that in 495 women, at a mean time of 2.3 postpartum years, 6.1% complained of significant pain related to delivery. A protective effect was observed following CS, while none of the other risk factors influenced the prevalence of PPP. Importantly, treatment of labour pain with either EA or RPCA had no effect on the occurrence of pain. One possible explanation for the lower incidence of PPP after caesarean section could be that postoperative treatment after caesarean section with epidural analgesia or opioids and thus effective analgesia protects from developing PPP. Our results further show important implications of PPP on the physical and mental health of the women in pain.

11

Nederlandse samenvatting

Dit proefschrift beschrijft de resultaten van de RAVEL trial (remifentanil patiënt gecontroleerde analgesie versus epidurale analgesie tijdens de bevalling). De RAVEL trial was een gerandomiseerde gecontroleerde equivalentie trial (N = 1358) die remifentanil patiënt gecontroleerde analgesie (PCA) en epidurale analgesie als pijnbestrijding tijdens de bevalling vergeleek. Omdat uit eerdere studies is gebleken dat, hoewel de epidurale analgesie superieur is aan remifentanil PCA in vermindering van pijn intensiteit scores, tevredenheid met analgesie vergelijkbaar leek te zijn, is deze studie opgezet als een equivalentie trial om gelijkwaardigheid aan te tonen in tevredenheid met pijnstilling. **Hoofdstuk 1** is een algemene inleiding waarin de meest relevante literatuur en achtergrondinformatie die de basis vormen van dit proefschrift worden samengevat.

Vóór aanvang van de RAVEL trial hebben we een online vragenlijst verstuurd om het gebruik van remifentanil PCA en epidurale analgesie in Nederland te evalueren en overtuigingen van gynaecologen en anesthesisten over pijnstilling te onderzoeken. De Nederlandse richtlijn 'Medicamenteuze pijnbestrijding tijdens de baring" adviseert om remifentanil PCA alleen te gebruiken in klinische studies en epidurale analgesie voor alle vrouwen 24/7 beschikbaar te hebben. Aangezien het gebruik van remifentanil PCA niet wordt geregistreerd in de Landelijke Verloskundige Registratie (LVR) en het onduidelijk was of epidurale analgesie in alle Nederlandse ziekenhuizen 24/7 beschikbaar is leek een vragenlijst de juiste wijze om deze vragen te beantwoorden. De resultaten van deze enquête worden gepresenteerd in **hoofdstuk 2**. Volgens officiële LVR gegevens kreeg 26,6% van de vrouwen in 2010 een vorm van medicamenteuze pijnbestrijding tijdens de bevalling (15% epidurale analgesie, 11,6% opioïden). 81% van respondenten van de vragenlijst gaf aan dat epidurale analgesie altijd beschikbaar was voor alle vrouwen op hun verzoek en in 92% indien er een medische indicatie voor epidurale analgesie bestond. Remifentanil PCA werd gebruikt in 44% van de opleidingsziekenhuizen en 55% van de niet-opleidingsziekenhuizen. Het gemiddelde gebruik van remifentanil PCA in deze ziekenhuizen was 23%. In ziekenhuizen waar alleen epidurale analgesie gebruikt werd was het gebruik van analgesie 20% (8-43%), terwijl in ziekenhuizen waar epidurale analgesie en remifentanil PCA beschikbaar waren het gebruik van analgesie 38% (26-63%) ($p < 0.001$) was.

Hoofdstuk 3 is het studie protocol voor de RAVEL trial zoals dat voor de start van de studie werd gepubliceerd.

Hoofdstuk 4 beschrijft de resultaten van de primaire onderzoeksvraag over de equivalentie in tevredenheid met remifentanil PCA in vergelijking met epidurale analgesie. Tevredenheid met pijn werd gemeten met behulp van een Visuele Analoge Schaal (VAS) gedurende de bevalling bij alle vrouwen en met deze seriële metingen werd een Area Under the Curve (AUC) berekend. De AUC voor tevredenheid met pijn tijdens de bevalling voor alle gerandomiseerde vrouwen was lager in de remifentanil PCA-groep (mean difference -2.8, 95% CI -6.9 tot 1.3). Dit kan een potentieel klinisch relevant verschil niet uitsluiten, daarom kunnen we niet concluderen dat de behandelingen equivalent zijn. Bovendien, in de subgroep van vrouwen die daadwerkelijk pijnstilling heeft

gekregen, was de AUC voor tevredenheid met pijn na aanvang van pijnstilling significant lager bij vrouwen met een verzoek voor pijnstilling gerandomiseerd voor remifentanil PCA (mean difference -10.4, 95% CI -13.9 tot - 7.0). Hetzelfde werd gezien in de AUC voor pijnintensiteit scores, deze waren significant hoger bij vrouwen gerandomiseerd remifentanil PCA. Vrouwen gerandomiseerd voor remifentanil PCA vroegen vaker om pijnstilling dan vrouwen gerandomiseerd voor epidurale analgesie (RR 1.3, 95% BI 1.2-1.5). Maternale en neonatale uitkomst verschilde niet significant tussen beide groepen. Sommige bijwerkingen werden vaker gemeld bij vrouwen die pijnstilling kregen. Maternale temperatuur was significant hoger en hypotensie kwam vaker voor in de epidurale analgesie groep. Zuurstof saturatie was significant lager bij remifentanil PCA. Er werden 4 ademhalingsdepressies gerapporteerd van <8 ademhalingen per minuut in de remifentanil PCA-groep en geen in de epidurale groep. Misselijkheid werd gemeld vaker voor in de groep gerandomiseerd voor remifentanil PCA, maar braken en jeuk waren gelijk.

Als onze hypothese klopte dat remifentanil PCA gelijk is aan epidurale analgesie wat betreft patiënt tevredenheid zou een kosten-effectiviteitsanalyse uitgevoerd worden. Omdat equivalentie niet werd aangetoond is een kosten analyse gedaan. **Hoofdstuk 5** beschrijft de resultaten van deze analyse. Gemiddelde kosten voor vrouwen gerandomiseerd voor remifentanil PCA waren € 2.900 versus € 3.183 voor vrouwen gerandomiseerd voor epidurale analgesie (mean difference - € 282 (95% CI - € 611 tot € 47)). Het grootste deel van dit verschil kan worden toegeschreven aan de hogere kosten van neonatale opname in de epidurale groep. Dit niet-significante verschil in kosten voor neonatale opname was -196 (95% BI -465 tot 73).
Na de inclusieperiode van de trial werd een Standard Operating Procedure (SOP) voor het gebruik van remifentanil PCA op de verloskamer ontwikkeld door de Inspectie voor de Gezondheidszorg (IGZ). Naar aanleiding hiervan werden post hoc scenario analyses verricht naar de invloed van de aanwezigheid van een anesthesioloog tijdens start van remifentanil PCA en de invloed van een continue 1 op 1 verpleging tijdens de toediening van remifentanil. Wanneer alleen de kosten van pijnstilling bekeken worden, nemen de kosten van remifentanil PCA toe wanneer een anesthesist aanwezig is bij aanvang van pijnstilling en nog meer met continue 1 op 1 verpleging. Alleen wanneer er geen anesthesist is betrokken bij de toediening van remifentanil PCA en er is 1 op 1 verpleging voor alleen het eerste uur is er een significant verschil in de kosten van pijnstilling in het voordeel van remifentanil PCA.

In **hoofdstuk 6** evalueren we respiratoire complicaties en temperatuur bij vrouwen die behandeld worden met remifentanil PCA en epidurale analgesie. In overeenstemming met andere gepubliceerde gegevens toonden we aan dat episodes van desaturatie vaker voorkomen en vrouwen een gemiddeld lagere SpO2 hebben bij het gebruik van remifentanil. Epidurale analgesie is geassocieerd met een hogere incidentie van koorts en hogere gemiddelde temperatuur. Remifentanil PCA heeft een effect op de maternale SpO2 met aanzienlijk lagere gemiddelde SpO2 tijdens de bevalling. Ook desaturatie <92% kwam meer voor in de remifentanil groep. Dit toont aan dat respiratoire complicaties een ernstig probleem zijn bij gebruik van remifentanil. Continue monitoring door getraind personeel wordt geadviseerd.

Na de publicatie van de RAVEL trial en de STER (Saturatie en Temperatuur in Epidurale analgesie en Remifentanil PCA) werd een meta-analyse van maternale parameters uitgevoerd. Hierin werden alle gepubliceerde gerandomiseerde gecontroleerde studies en observationele studies die de werkzaamheid en bijwerkingen van remifentanil vergeleken met andere pijnstilling meegenomen. De resultaten staan in **hoofdstuk 7**. Er werd een duidelijke trend naar meer desaturatie waargenomen tijdens de toediening van remifentanil PCA in vergelijking met andere opioïden, hoewel de resultaten zijn niet significant verschillend zijn. In vergelijking met epidurale analgesie waren er significant meer episodes van desaturatie (SpO2 <95%) tijdens de toediening van remifentanil PCA. Bovendien werd er meer maternale sedatie gezien bij gebruik van remifentanil PCA ten opzichte van epidurale analgesie en meer jeuk bij gebruik van remifentanil in vergelijking met andere opioïden. Er leek geen verschil in ademhalingsdepressie (<8) of hypotensie te zijn, maar deze incidenten zijn zeldzaam en werden slecht gemeld. Er waren geen verschillen in cardiotocografie, Apgar scores en de wijze van bevallen tussen de groepen. Gezien de respiratoire complicaties wordt strikte observatie van vrouwen die worden behandeld met remifentanil, in het bijzonder continue saturatiemeting en de beschikbaarheid van basic life support, sterk aanbevolen.

Vrouwen die deelnamen aan de RAVEL trial werden retrospectief benaderd voor een onderzoek naar de prevalentie van chronische pijn post partum (PPP), waarbij de pijn begonnen is rondom de bevalling. Het doel van deze studie was de prevalentie van PPP in een Nederlands cohort te onderzoeken en specifieke risicofactoren en de invloed van pijnstilling bij de ontwikkeling van chronische pijn na de bevalling te evalueren. De resultaten van deze studie worden gepresenteerd in **hoofdstuk 8**. Van 495 vrouwen met een mediane duur van 2,3 jaar postpartum, ervoer 6,1 % significante pijn die verband hield met de partus. In vergelijking met een spontane bevalling beschermde een keizersnede tegen PPP. Een mogelijke verklaring hiervoor is dat de postoperatieve pijnstilling na keizersnede met epidurale analgesie of opioïden, en dus adequate pijnstilling, beschermt tegen het ontwikkelen van PPP. Onze resultaten tonen verder dat PPP belangrijke gevolgen heeft voor de lichamelijke en geestelijke gezondheid van vrouwen met pijn.

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Freeman LM, Douma MR, Arbous MS, Dahan A, Middeldorp JM. Maternal temperature and oxygen saturation in women using remifentanil patient controlled analgesia and epidural analgesia for pain relief during labour; a sub analysis of the RAVEL trial. Submitted.

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Curriculum Vitae

Liv Marije Freeman was born by secondary caesarean section on September 12th 1979 in the old Antonius Ziekenhuis in Utrecht. She wanted to be a doctor from a very young age and wanted to be a neonatologist after her youngest sister was born (1990). She graduated from the St. Bonifatiuscollege, Utrecht (gymnasium) in 1997.

After graduation she moved to Maastricht to study at the Medical Faculty of the University of Maastricht. As a student she was a very active member of Studentenvereniging KoKo. Before starting her internships she travelled through Venezuela for 2 months. Her scientific research internship regarded the expression of MMPs in endometriosis (Dr. A.W. Nap). In her final year she did an internship at the Royal Flying Doctor Service in Broken Hill Australia. Combining her long existent love for neonatology with a newfound love for surgery during her surgical internship made her pursue a career in gynaecology and obstetrics.

After graduating (cum laude) from medical school in 2004 she started working as a physician (ANIOS) in the Meander Hospital in Amersfoort and in 2005 in het HagaZiekenhuis in Den Haag. In 2007 she started residency at the HagaZiekenhuis (Dr. E. van Rijssel) and continued at the LUMC (Prof. Dr. J. van Lith) and HagaZiekenhuis (Dr. B. Hellebrekers). In 2010 she was given the opportunity to coordinate the RAVEL trial (remifentanil patient controlled analgesia versus epidural analgesia in labour) of which the results led to this thesis. After finishing her residency in 2013 she started a fellowship in perinatology at the LUMC.

She lives in The Hague with her son Jonas (2014).

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