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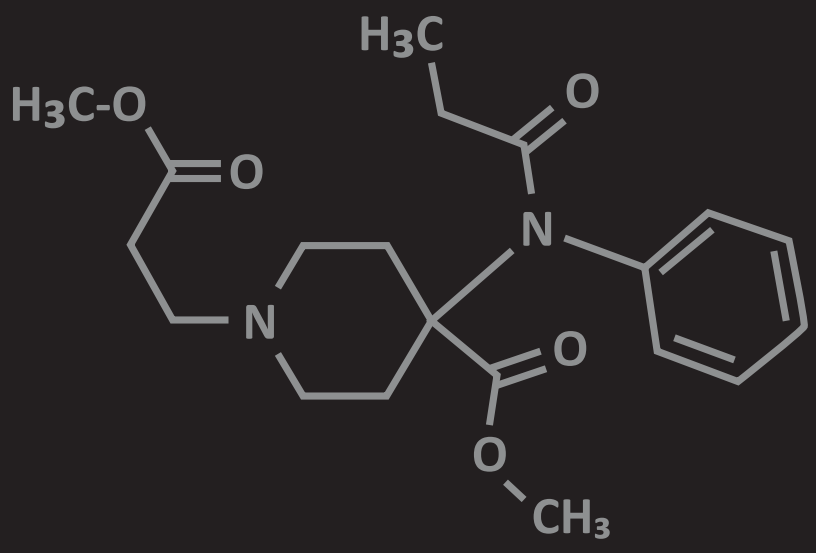

Sabine Logtenberg

REMIFENTANIL FOR LABOUR ANALGESIA

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COLOFON

Remifentanil for labour analgesia
Thesis, University of Amsterdam, the Netherlands

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REMIFENTANIL FOR LABOUR ANALGESIA

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CHAPTER 1

General introduction

INTRODUCTION

Pharmacological pain relief during labour, specifically remifentanil patient controlled analgesia, is the main subject of this thesis. Additionally we studied the recruitment of pregnant women for participating in randomised controlled trials. This chapter includes a general introduction for both subjects.

Labour pain

Childbirth is associated with labour pain. The definition of pain was introduced by The International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1). Labour pain is considered as a very severe pain (2). During the first stage of labour uterine contractions and cervical dilatation cause visceral pain transmitted via nerve roots T10 to L1. In the second stage of labour distention of the vagina, perineum, pelvic floor and stretching of the pelvic ligaments also contributes to the experienced labour pain, transmitted through nerve roots S2 to S4 (3,4). Women report three types of labour pain: abdominal contraction pain, intermittent low back pain and continuous low back pain (5). Usually pain intensity increases during the process of labour, the strongest labour pain is often experienced when the dilatation progresses between eight to ten centimetres (6).

In contrast to other acute or chronic pain labour pain is physiological (6). From a biological point of view labour pain can be considered as a warning sign for the woman and the people around her that she is going to give birth for which she has to find a safe place (6). Women's experiences of labour pain vary greatly and are influenced by the physiological and psychological processes of birth and the extent to which women perceive pain (7). Factors as parity, anxiety, self-efficacy, cultural background, coping strategies, birth environment and care practices influence -probably interrelated- the experienced pain intensity (6,8). Although labour pain is primarily not pathological, it might be associated with adverse effects on the mother and indirectly the neonate (6,8,9). Psychological effects of labour pain may include exhaustion, anxiety and depression. Physically adverse effects may include increased oxygen consumption, hyperventilation –an initially a physiologic phenomenon- which could lead to hypocarbia and respiratory acidosis, elevated plasma cathecholamine levels which could deteriorate uterine contractility, gastric inhibition, increased peripheral vascular resistance; increased cardiac output, increased blood pressure and decreased placental perfusion. These effects may be within normal ranges in uncomplicated labour (6,8,9).

Pain relief during labour

Current practice in the Netherlands

Historically, labour pain has been considered as a normal aspect of childbirth in the Netherlands (10). Women at low risk for obstetric complications start labour in primary midwife-led care. A request for pharmacological pain relief –other than nitrous oxide- is an indication for referral to hospital-based obstetric-led care. In The Netherlands, a request for pharmacological pain relief is -since several years- the most frequent reason for a referral from primary midwife-led care to hospital-based obstetric-led care during labour. Pharmacological pain relief was accountable for 18% of all referrals during labour in 2017, even more than referrals for meconium stained fluid or failure to progress, which accounted for respectively 16% and 12% of the referrals. The percentage of women receiving epidural analgesia during labour increased in The Netherlands in the last decade from 8.2% in 2006 to 22% in 2016 (11). The use of remifentanil patient controlled analgesia (PCA) as a labour analgesic is not included in the Dutch Perinatal Registry (PRN), Perined, a national linked database in which data of 98% of all births in the Netherlands are recorded (11). Therefore, the current practice of remifentanil-PCA use is unknown.

The Dutch maternal care system is characterised by differences in context in which women receive prenatal and intrapartum care, either in primary midwife-led care or hospital-based obstetric-led care. Birth environment and care practices could influence the need for pharmacological pain relief. A recent WHO recommendation states that ''Health care professionals should be aware that women's desire for epidural analgesia might be moderated by the clinical context in which they receive antenatal and intrapartum care, whether labour is spontaneous or not, and their access to and knowledge of a range of other forms of pain relief measures. It is likely that the care context, the type of care provision and care provider have an effect on the need for labour pain relief, and on the kinds of choices women make in relation to this need" (12). Pain management strategies aim to help women to cope and/or to relieve labour pain. One could distinguish non-pharmacological pain relief and pharmacological pain relief (7).

Non-pharmacological pain relief

There is a variety of non-pharmacological methods available for pain relief during labour like immersion in water, relaxation, acupuncture, massage, hypnosis, biofeedback, sterile water injection, aromatherapy and transcutaneous electrical nerve stimulation (TENS)(7). Advantages of non-pharmacological methods are the availability independent of the place of birth, their non-invasive nature and safety for both the woman and the neonate. Although non-pharmacological interventions could help women to cope with labour pain, there is a lack of evidence for the efficacy of many non-pharmacological interventions to relief labour pain. In a Cochrane review by Jones et al. only some evidence for pain relief with non-pharmacological strategies as immersion in water, relaxation, acupuncture and massage was found (7). Another important

intervention is continuous one-to-one support during labour. Historically, women have been attended by other women during childbirth to receive emotional support, information and advice. Currently continuous one-to-one support is - especially in hospital circumstances- not self-evident. There is evidence that women who receive continuous one-to-one support during labour are less likely to need intrapartum analgesia (13). From that point of view continuous one-to-one support during labour could be considered as an effective non-pharmacological strategy to help women to cope with labour pain (13).

Pharmacological pain relief

Nowadays, guidelines state that a maternal request for pharmacological pain relief is sufficient medical indication for pharmacological pain relief during labour (2,7,10,12). Pharmacological pain relief reduces the pain experienced during labour and is indicated when a woman has either a primary request for pain relief or a secondary request, if non-pharmacological interventions are insufficient (2,6,7,10). Pharmacological methods of pain relief are widely used during labour with a variation in the percentage of women using pain relief. The percentage of women using pharmacological pain relief depends on factors as parity, culture, ethnicity, education level, birth environment, care practice and the country (2,7). Multiple pharmacological strategies are available such as epidural analgesia, inhaled analgesia and parenteral opioids.

Epidural analgesia

The introduction of neuraxial analgesia into obstetric practice took place at the end of the 19th century although it was rarely used at that time. Several improvements in epidural analgesia – e.g. the introduction of safety regulations- occurred in the 1970s and 1980s and since that time this method of labour analgesia has been used worldwide (14). Epidural analgesia is the most effective method of pain relief during labour (2,7,10). With epidural analgesia, in the lower region of the spine an epidural catheter is threaded through a needle into the epidural space and connected to an infusion pump system. A local anaesthetic -commonly in combination with an opioid- is administered through the epidural catheter to provide a central nerve block by closing the nerves that transmit pain. Continuous epidural and combined spinal–epidural (CSE) are the most commonly used neuraxial techniques for labour analgesia. Epidural analgesia is associated with an increased risk of maternal hypotension, itching, motor-nerve blockade, maternal fever and urinary retention postpartum. Disadvantages of epidural analgesia are the dependence of the availability of an anaesthesiologist, contraindications like HELLP syndrome, coagulation- or skeletal disorders and possible side effects (7,15). Alternative methods for pain relief are desired if epidural analgesia is not available, not preferred or contraindicated (16).

Inhaled analgesia

Inhaled analgesia, was first introduced as labour analgesia in 1847. Nowadays, nitrous oxide (N_2O) is the most commonly used inhaled analgetic. Other inhaled analgetics -most suitable

for labour analgesia- are enflurane, isoflurane and methoxyflurane (17). Nitrous oxide, a mix of 50% nitrous oxide in 50% oxygen, is self-administered by labouring women by inhalation through a mouthpiece or facemask. A demand valve ensures that the woman only inhales the gas when using the mask and equipment to minimise environmental contamination has to be used. The precise mechanism of action of pain relief by inhaled analgesia remains uncertain (2,17). Previous research showed adverse side effects of nitrous oxide - reproductive failure- in female maternity care professionals. Since improvement of the equipment and the availability of well-ventilated delivery rooms the exposure to nitrous oxide is minimised and the risk of reproductive failure is eliminated (17). Benefits of nitrous oxide are e.g. its ease of administration, there is no additional monitoring required and there is no effect on uterine contractions. Contra indications for nitrous oxide are vitamin B12 or folic acid deficiency and it is associated with nausea, dizziness, drowsiness and vomiting. In a Cochrane review Klomp et al. compared different types of inhaled analgesia with placebo, another type of inhaled analgesia or TENS. They concluded that inhaled analgesia may be beneficial for those women in labour who want to have some form of pharmacological pain relief without invasive methods (7,17).

Opioids

The first documentation of opioid use in labour appeared in ancient Chinese writings (18). Parenteral opioids, administered either by intramuscular injections or intravenous infusions, are often used in maternity units. Worldwide pethidine, also known as meperidine or demerol, has been introduced in the early 1940s and is the most commonly used opioid (18–20). Other opioids used for labour analgesia are diamorphine, nalbuphine, butorphanol, meptazinol, pentazocine, fentanyl, morphine, tramadol and remifentanil. The analgesic effects of opioids are a result of the activation of opioid receptors, specifically μ-opioid receptors. Opioids readily cross the placenta by passive diffusion. This may cause side effects in the neonate: within one to three hours after maternal administration of pethidine there is an increased risk for neonatal respiratory depression with birth. It is estimated that it can take a neonate three to six days to eliminate pethidine, and its metabolite, norpethidine, from its metabolic system (7). Maternalside effects include nausea, vomiting and drowsiness (21). Advantages of opioids are the ease of administration, the wide availability, and opioids are inexpensive and less invasive than epidural analgesia. In a Cochrane review Ullman et al. compared different types of opioids with placebo, another opioid or TENS. They concluded that opioids in general provide some pain relief, no evidence was found which opioid is the best. Besides, maternal satisfaction with the use of opioid was underreported (21).

Remifentanil patient controlled analgesia

The relatively new drug remifentanil has been first described in 1991 (22). Remifentanil is a synthetic opioid, has a fast onset of action (30-60 seconds) and is rapidly metabolised through tissue esterase to inactive metabolites. An important advantage of remifentanil is its short half-

life (3 minutes). It crosses the placenta but it is metabolised and redistributed quickly by the fetus (23,24). These unique properties make remifentanil a popular option for labour analgesia. Remifentanil patient controlled analgesia (remifentanil-PCA) could be an alternative for epidural analgesia, although (combined spinal) epidural analgesia is superior to remifentanil-PCA with regard to pain relief (16,24–27). Remifentanil-PCA is less invasive than epidural analgesia and the restrictions for epidural analgesia do not apply for remifentanil-PCA. Compared to other opioids, either intramuscular, intravenous or PCA, pain scores at one hour are lower for remifentanil-PCA (16). Schnabel et al. concluded that satisfaction with pain relief during the use of remifentanil-PCA compared to satisfaction with pain relief during epidural analgesia was underreported (27).

Possible side effects of remifentanil are nausea, pruritus, desaturation, chest wall rigidity, hyperalgesia, respiratory depression and apnea (23,28–30). Respiratory depression –in the woman or the neonate- is a major concern. Since 2012 several case reports have been published in which maternal respiratory arrest and/or cardiac arrest occurred as a result of remifentanil-PCA (31–33). Recently nine cases of maternal respiratory depression – of which two resulted in cardiac arrest - were identified in a survey among academic medical centres in the United States by Aaronson et al. (34). The Swiss RemiPCA SAFE Network, a centralised database for remifentanil-PCA usage since 2009, registered more than 7,000 applications with remifentanil-PCA in 39 hospitals without any case of assisted ventilation or resuscitation of the mother registered (35,36). Although neonatal respiratory depression due to remifentanil-PCA seems to be rare, neonatal resuscitation after remifentanil-PCA has been described (24–26,37,38). Recently Aaronson et al. found five cases of neonatal complications due to remifentanil-PCA (34). These differences in complications due to remifentanil-PCA might be explained by variations in protocols, for example continuation or discontinuation of remifentanil-PCA during the second stage of labour. So far, the incidence of adverse maternal and neonatal outcomes remains unknown. A recent Cochrane review concluded that complications as maternal apnea and/or cardiac arrest and neonatal respiratory depression as a result of remifentanil-PCA use are underreported (16).

Remifentanil-PCA is not registered for labour analgesia and therefore using it during labour is considered as off-label use worldwide (39). Nonetheless, remifentanil-PCA is frequently used for pain relief during labour - mainly in Europe - the past two decades (19,20,27,40). Although the Dutch guideline “Medical pain relief during labour” recommended the use of remifentanil-PCA only in a research setting, visits of The Dutch Health Care Inspectorate at obstetric wards in 2012 and 2013 showed that remifentanil-PCA was introduced on a large scale with a variety of protocols in The Netherlands (10,41). Previous research also showed a variety of protocols for the administration of and maternal monitoring during remifentanil-PCA (16,27,40). Differences in administration regimens have been described for each bolus, adjusted to patient’s body weight (0,25-0,5µg/kg) or a scheme with increasing doses (20-40µg) depending on efficacy; whether or not combined with background infusion and lock-out times between one to five

minutes (16,40). Different protocols with continuous or intermittent measurements are being used for the maternal monitoring. These measurements could include maternal oxygen saturation, blood pressure, pulse rate, respiratory rate, end tidal CO_2, sedation score and the presence or absence of continuous one-to-one care. The RemiPCA SAFE Network provides standard operating procedures -concerning dosing and monitoring during remifentanil-PCA- for participating hospitals (36). In The Netherlands, the variety of protocols for the administration of remifentanil-PCA in Dutch hospitals have led to the requirement of The Dutch Health Care Inspectorate to use a multidisciplinary Standard Operating Procedure (SOP) for the use of remifentanil to control labour pain. The SOP was composed and introduced by the Dutch Societies of Obstetrics and Gynaecology, Midwifery, Anaesthesiology and Hospital Pharmacists in 2014 (42). Although the SOP requirements for maternal monitoring appoints, there is currently no consensus towards the ideal maternal monitoring necessary for the safe administration of remifentanil-PCA (28,43,44). The safety concerns mentioned make remifentanil-PCA a controversial method for pain relief (28,40,45). Proponents state that remifentanil-PCA should be routinely available and opponents state that remifentanil-PCA remains a highly controversial analgesic technique (28,44,46,47).

Pharmacological pain relief in relation to childbirth satisfaction

There is a complex relation between labour pain, pain relief and satisfaction with childbirth. Labour pain and pain relief influence satisfaction with childbirth. However satisfaction with childbirth is most influenced by personal expectations, the amount of support from caregivers, the quality of the caregiver-patient relationship, continuous support of labour and involvement in decision making (13,48,49). Other aspects of childbirth satisfaction are coping with labour pain and having a choice in labour analgesia (48,50). Pharmacological pain relief does not always result in a better childbirth experience, nor does it necessarily improve the mother's well-being (6,50,51). Rijnders et al. found that women who did not experience a choice in pain relief or women who were dissatisfied with their pain coping mechanism, had – respectively - an almost three and five times higher chance of a negative recall three years after birth (48). Similarly, pain relief and satisfaction with pain relief are not the same, although some researchers have equated them (50). Patient preferences, experiences and satisfaction have become more important for policymakers and health care providers (12,41). Currently these aspects are considered to be an important aspect in guidelines, protocols and are taken into account for the availability of treatment options (12,52,53). In this light, having a choice in labour analgesia and satisfaction with pain (relief) are relevant.

Recruitment of pregnant women in clinical trials

A relevant topic in the randomised controlled trials we report in this thesis was the recruitment of pregnant women. Randomised controlled trials in pregnant women are unique, since two individuals are involved: the mother and her unborn fetus. Recruitment of pregnant women

seems even more difficult than recruitment of patients in general. A woman may refuse treatment for herself if she feels this could harm her baby, or she may feel bound to accept interventions that might benefit the fetus. Earlier research showed that recruitment was influenced by factors as: understanding risk, recruitment process and procedures, participants' understanding of the research process and methodological issues, and patient characteristics (54). These factors were identified as barriers from studies that had failed to recruit a sufficient number of participants. It is unknown to what extent these results also apply to other studies, regardless of recruitment performance.

Aim of the thesis

Pain relief during labour is a complex theme. In case of a request for pharmacological pain relief an individual balance between all aspects of pain relief has to be made. A combination of choices between the efficacy, side effects and availability of the treatment options, women's preferences and labour characteristics will influence the decision which method of pain relief is most suitable for the woman. To provide adequate labour analgesia with remifentanil-PCA while preserving maternal and neonatal safety regulations is a challenge. The central aim of this thesis is therefore to contribute to the possible place of remifentanil-PCA for labour analgesia, both from the perspective of the women and the health care providers.

We have studied the following questions:

1. Does remifentanil-PCA provides equivalent satisfaction with pain relief compared to epidural analgesia and what is the association between remifentanil-PCA, epidural analgesia and fear of childbirth?
2. What is the practice variation of remifentanil-PCA use and the number of serious adverse events attributed to the use of remifentanil-PCA for labour analgesia in The Netherlands?
3. Which labouring women needing pain relief will be satisfied with remifentanil-PCA and which women with epidural analgesia?
4. What are the main barriers and motivators of pregnant women for enrolment in obstetric trials in The Netherlands?

OUTLINE OF THE THESIS

Chapters 2 & 3 report the results of two randomised controlled equivalence trials (RAVEL) comparing satisfaction with pain relief during remifentanil-PCA versus epidural analgesia respectively in women with a low and intermediate to high obstetric risk. The trials were conducted in 18 midwifery practices and 15 hospitals in The Netherlands.

Chapter 4 describes a secondary analysis of the RAVEL study to assess the association between fear of childbirth antepartum and a request for pharmacological pain relief and between

the used method of pain relief –remifentanil-PCA or epidural analgesia- and fear of childbirth reported postpartum.

Chapter 5 provides the results of a survey among gynaecologists in all 81 Dutch hospitals with a delivery ward to determine the practice variation of remifentanil-PCA.

Chapter 6 reports the results of a survey among gynaecologists, anaesthetists and clinical midwives in all 59 hospitals using remifentanil-PCA for labour analgesia. The survey examined the number of serious adverse events attributed to the use of remifentanil-PCA for analgesia during labour in The Netherlands.

Chapter 7 describes a secondary analysis of both RAVEL studies to identify potential markers to predict which women will be satisfied with remifentanil-PCA and which women with epidural analgesia.

Chapter 8 reports the analysis of recruitment in randomised clinical trials at the level of the patient. We performed semi-structured interviews with 21 women invited to participate in a trial in obstetrics.

Chapters 9 contains the summary and general discussion of the thesis in respectively English and Dutch.

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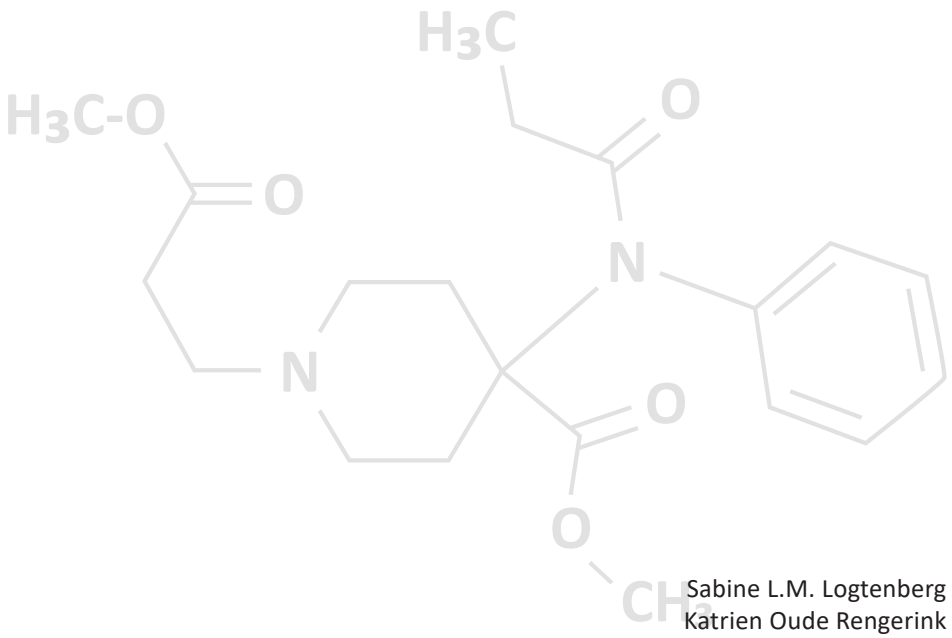
CHAPTER 2

Labour pain with remifentanil patient controlled analgesia versus epidural analgesia; a randomised equivalence trial



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ABSTRACT

Objective	To distinguish satisfaction with pain relief using remifentanil patient controlled analgesia (RPCA) compared to epidural analgesia (EA) in low-risk labouring women.
Design	Randomised controlled equivalence trial.
Setting	Eighteen midwifery practices and six hospitals in The Netherlands.
Population	A total of 408 pregnant women at low risk for obstetric complications initially under the care of primary care midwives.
Methods	Women randomised before active labour to receive analgesia with RPCA or EA, if requested.
Outcome measures	Primary outcome was satisfaction with pain relief measured hourly using a visual analogue scale and summed as area under the curve (AUC). Secondary outcomes were overall satisfaction with pain relief, pain intensity scores during labour, mode of delivery and maternal and neonatal outcomes.
Results	We randomised 418 women, of whom 409 women could be followed for the primary endpoint. Analgesia was received by 46% (94/203) in the remifentanil group and 37% (76/206) in the epidural group. The AUC for satisfaction with pain relief was 32 in the remifentanil group and 31 in the epidural group (mean difference -0.50; 95% CI -6.8 to 5.9). Among women who actually received analgesia, these values were 23 and 35 respectively (mean difference -12; 95% CI -22 to -1.5). Secondary outcomes were comparable.
Conclusions	In low-risk labouring women, we could not demonstrate equivalence between a strategy with RPCA to EA with respect to satisfaction with pain relief assessed during the total duration of labour. However, once applied satisfaction was higher in women who received epidural analgesia.

INTRODUCTION

Although epidural analgesia (EA) is the most effective method of pain relief during labour, it is invasive: EA increases the risk of assisted delivery and has an increased risk of maternal fever, maternal hypotension and urinary retention (1–3). Remifentanil - a synthetic opioid- has a fast onset of action, a short half-life and is metabolised and redistributed quickly by the fetus (4,5). Intravenous remifentanil patient controlled analgesia (RPCA) offers an alternative to EA, but is associated with desaturation and respiratory depression (4). Involvement in decision making and having a choice in labour analgesia are important aspects of childbirth satisfaction (6–8). Previous trials found comparable satisfaction with pain relief by RPCA and by EA, while they showed that EA is superior to RPCA with regard to pain scores (9–14).

To allow women to make informed choices concerning pain relief, larger trials are needed (15). Recently, we published the RAVEL study that compared RPCA and EA for satisfaction with pain relief among women with a medium to high obstetric risk. This trial found comparable results for all women in the trial whether or not they requested pain relief, whereas satisfaction scores for pain relief in women who received analgesia were better after EA (16).

To our knowledge, the strategies with RPCA and EA have never been compared in a group of only low-risk labouring women initially under the care of primary-care midwives. The aim of our study was to test the hypothesis that RPCA provides equivalent satisfaction with pain relief when compared with EA, using a visual analogue scale (VAS), in women with a low obstetric risk.

METHODS

We performed an open label randomised controlled equivalence trial in 18 midwifery practices in The Netherlands, positioned within the Dutch Obstetric Consortium for women's health research. The protocol was approved by the ethics committee of the University Medical Centre Leiden and the boards of the six participating hospitals.

In the Netherlands, healthy pregnant women start antenatal care in primary, midwifery-led, care. Women are considered low risk if their medical and obstetric history is uneventful and they have an uncomplicated pregnancy. Women beyond 32 weeks gestation under the care of primary care midwives were eligible. Women younger than 18 years, women with a contra-indication for epidural analgesia or a hypersensitivity to opioid and women in whom labour had already started were not eligible.

Women were informed about the study by their midwife and after written informed consent was obtained, they were randomly allocated to a strategy with RPCA or EA in a 1 : 1 ratio, in case they should request pain relief during labour. Randomisation- always before the onset of labour- was performed using a web-based randomisation program stratified for midwifery

practice and parity. Both the woman and the midwife knew the randomisation allocation in case a request for pain relief should occur during labour. Not all women received analgesia, as analgesia during labour was given only when it was requested by the women. If women requested pain relief during labour, or if medical complications occurred either before or during labour, women were referred from midwife-led primary care to obstetrician-led secondary care.

Women randomised to RPCA received intravenous remifentanil 30-µg boluses (solution 20 µg/ml) with a lockout time of 3 minutes and without background infusion. A doctor or a midwife and a nurse were responsible for providing and monitoring the RPCA. The RPCA was administered by the parturient herself after instruction how to use RPCA in the most beneficial way, which is to use the bolus dose just before the anticipated contraction. It was possible to increase the bolus dosage to 40 µg in case of insufficient pain relief, or to decrease the dose to 20 µg in case of excessive side effects.

Women randomised to epidural analgesia received EA with a loading dose of 25 mg (12.5 ml ropivacaine 0.2%) and continuous infusion of ropivacaine 0.1% plus sufentanil 0.5 µg /ml was administered. Continuous infusion was used at a variable rate defined by the anaesthetist and the local protocol. Additional boluses were used for inadequate levels of analgesia.

If analgesia with the randomly allocated pain method was insufficient according to the woman, a switch to the other trial arm was allowed.

Maternal satisfaction with labour pain scores and pain intensity scores were assessed hourly from the start of active labour until the second stage of labour in all participating women. Active stage of labour was defined as presence of regular, painful uterine contractions at regular intervals of 2-3 minutes with cervical dilation.

Women were asked to rate their level of satisfaction with labour pain on a ruler with a VAS ranging from 0 to 10 cm (highly dissatisfied or satisfied regarding the pain respectively). The question was specifically to judge a pain satisfaction score during active labour, not to be confused with satisfaction of childbirth. At the same time women were asked to rate their level of pain intensity on a scale ranging from 0 (no pain) to 10 cm (worst pain imaginable). In case women were using analgesia they were asked to rate their satisfaction with pain relief instead of satisfaction with labour pain. Maternal vital parameters and fetal heart rate were continuously monitored in women receiving pain relief. When oxygen saturation dropped below 95% oxygen was given.

The primary outcome was satisfaction with pain relief during labour expressed as area under the curve (AUC), which is a summary measure that integrates serial VAS assessments of a woman's satisfaction with pain relief from the start of analgesia until the second stage of labour and over the total time period of active labour. The AUC could be calculated if at least two pain satisfaction scores were recorded (17).

Secondary outcomes were the AUC for pain intensity scores during labour; overall satisfaction with pain relief and pain intensity score assessed by the women 2 hours and 6 weeks after delivery. Other secondary outcomes were conversion to other methods of analgesia, time from

request for pain relief to start analgesia, duration of analgesia and of the second stage of labour, mode of delivery, maternal desaturation (<92%), maternal morbidity (post spinal headache, postpartum haemorrhage (≥1000 ml in the 24 hours after delivery or administration of blood products), suspected infection (defined as a temperature >38^{o} C and/or use of antibiotics), uterine rupture, eclampsia, amniotic fluid embolism and myocardial infarction, admission to ICU), Apgar scores after 5 minutes < 7, postpartum maternal and neonatal admission in the hospital and diagnosis during admission.

The trial was an equivalence trial in which the null hypothesis was that the difference in satisfaction with pain relief score, scored on a 0- to 10-point VAS, between the two treatment groups was not equivalent. We assumed that a 10% difference would be clinically relevant in accordance with the RAVEL trial (16). With 204 women we would have 80% power to reject the null hypothesis that the treatments are not equivalent and accept the alternative hypothesis that the proportions in the two groups are equivalent, using a 0.05 risk of type I error (two-sided test). We estimated that about 50% of participants would request pain relief. Therefore 408 women had to be randomised.

Before any analysis, we amended the protocol in February 2013 because we decided to change the primary outcome from a score at one time-point to the AUC, which integrates all VAS and it can deal with missing values. Our sample size calculation was performed on a different outcome parameter. In the sample size calculations, we used 10% reduction on the pain satisfaction VAS scale as an equivalence margin, which is one point reduction in pain satisfaction. Since 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.

Data were analysed on an intention-to-treat basis. We assessed equivalence with a two-sided 95% confidence interval around the estimate of the difference between the AUC satisfaction scores between the groups. Secondary outcomes were analysed for superiority. Continuous variables were summarised as means with standard deviations or medians with interquartile ranges if not normally distributed, and compared using the Student's *t*-test or the non-parametric Mann-Whitney *U* test, respectively.

For categorical data, the treatment effect was presented as relative risk with 95% confidence intervals and the χ^2 test was used to test for statistical differences. If the expected cell count was <5, we used the Fisher's exact test. Calculation of the percentages was based on the number of valid observations. Multiple imputation was used to account for missing primary outcome data. Missing AUC scores for satisfaction with pain relief and pain intensity were imputed 20 times, based on both the predictor variables (age, parity, gestational age, education level, body mass index, onset of labour, duration of analgesia, duration of second stage of labour, duration of admission hospital) and the outcome (17,18). Other missing values were not imputed.

Additional analyses were planned for women who did or did not receive analgesia; for nulliparous and multiparous women. Per-protocol analysis was planned for the group who

received analgesia. We used SPSS version 22 (SPSS Inc., Chicago, IL, USA) for all analyses. *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Between November 2012 and June 2013, we randomised 418 women. We analysed the data of 409 women, of whom 203 women had been allocated to the RPCA group and 206 women to the EA group (Figure 1).

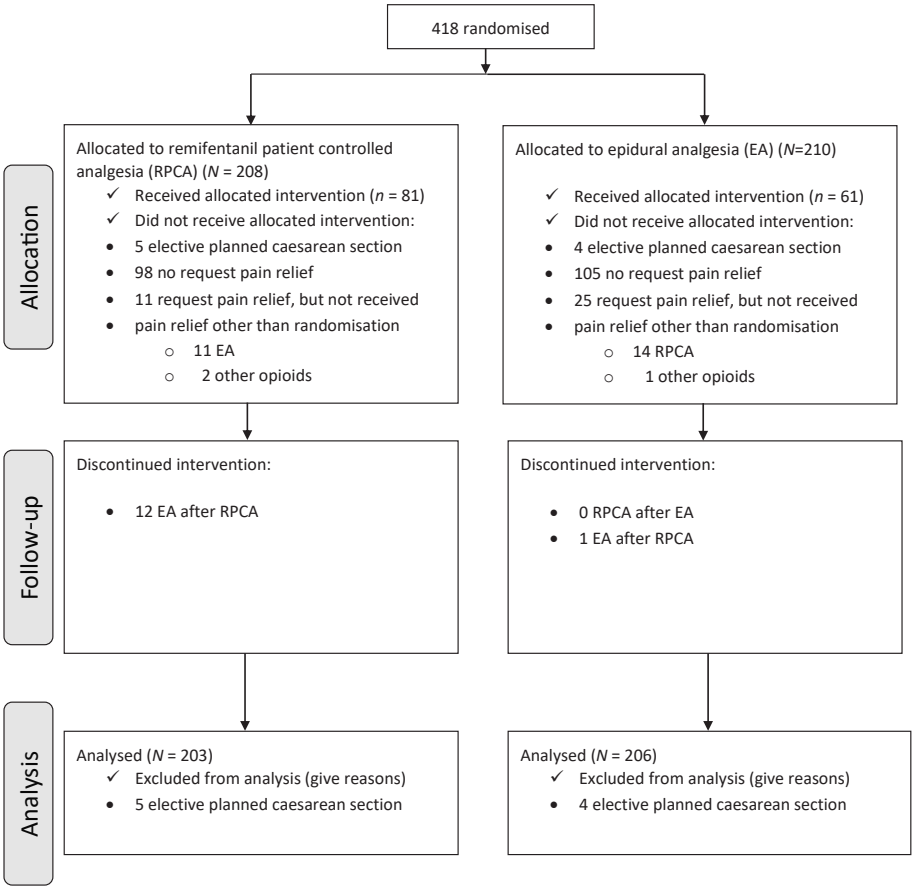

Figure 1. Flowchart

Nine women had an elective caesarean section planned after randomisation, and these women were excluded from the analysis. Baseline characteristics were comparable between the groups (Table 1).

Table 1. Baseline characteristics at randomisation

	RPCA *n* = 203	Epidural *n* = 206
Gestational age (weeks), median (IQR)	36.1 (34.3-37.6)	36.1 (33.9-37.7)
Maternal age (years), mean (SD)	31.7 (3.9)	31.8 (4.2)
Ethnic origin (%)		
White	182 (90)	190 (92)
Non-white	21 (10)	16 (8)
Education ≥ higher (high school & university)(%)	156 (77)	158 (77)
Missing	7 (3)	7 (3)
Body mass index (kg/m^2) mean (SD)	22 (3.4)	
Parity (%)		
0	138 (68%)	146 (71)
≥1	65 (32%)	60 (29)

IQR, interquartile range; SD, standard deviation

In the RPCA group 105/203 (52%) women requested pain relief, compared to 101/206 (49%) in the EA group. Of these women 94/203 (46%) in the RPCA group actually received analgesia, compared to 76/206 (37%) women in the EA group (Table 2).

Table 2. Primary outcome: mean area under the curve for satisfaction with pain relief and pain intensity scores during active labour and after start analgesia

	RPCA *n* = 203	Epidural *n* = 206	*P*-value
Request pain relief (%)	105 (52)	101 (49)	0.59
Received pain relief (%)	94 (46)	76 (37)	0.05
Mean area under the curve	**AUC**	**AUC**	**Risk Difference (95%CI)**
Satisfaction with pain relief			
During active labour	31	31	-0.50 (-6.8 to 5.9)
During active labour with missing AUC values imputed	32	31	0.52 (-5.5 to 6.6)
During analgesia (94 RPCA; 76 EA)*	23	35	-12 (-22 to -1.5)
During analgesia with missing AUC values imputed	23	35	-12 (-22 to -1.7)
Pain intensity score			
During active labour	39	33	6.4 (0.3 to 13)
During active labour with missing AUC values imputed	40	33	7.0 (1.2 to 13)
During analgesia (94 RPCA; 76 EA)*	29	17	12 (3.0 to 21)
During analgesia with imputation of missing AUC values	29	17	12 (2.1 to 22)

*number of women that did receive pain relief

In the RPCA group, reasons for not receiving analgesia despite request were vaginal delivery before RPCA was in place (*n* = 8), an emergency caesarean (*n* = 1) while for two women an anaesthetist was not available after a preference of the care giver for EA. In the EA group, reasons for not receiving analgesia despite request were delivery before EA was in place (*n* = 22); no availability of an anaesthetist (*n* = 2) and a delayed result of platelets checked because of hypertension (*n* = 1).

In the RPCA group, 81/94 (86%) who requested pain relief received RPCA; 11 started with EA despite randomisation for RPCA and two used other opioids. In the EA group, 61/76 (80%) who requested pain relief received EA, 14 started with RPCA despite randomisation for EA and one used other opioids. In the RPCA group, 12/81 (15%) women switched to EA after the start of RPCA. In the women converted to EA 11/12 women were nulliparous and 9/12 women had ≤ 4 cm dilatation at request pain relief. In the EA group one nulliparous woman who started RPCA at own request switched to EA at 4 cm dilatation (Figure 1).

The AUC for satisfaction with pain relief during active labour could be calculated- at least two scores available- for 167/203 (82%) women of the RPCA group and for 141/206 (68%) women of the EA group. The AUC for pain intensity score during active labour could be calculated for 170/203 (84%) women of the RPCA group and for 143/206 (69%) of the women of the EA group. We performed an imputation for the endpoint for pain satisfaction in 36/203 women of the RPCA group and 65/206 of the EA group for the AUC. The observed value of the AUC for satisfaction with pain relief was comparable between the groups but equivalence could not be demonstrated statistically (difference 0.52; 95% CI -5.5 to 6.6). In the subgroup of women who received analgesia, satisfaction with pain relief was significantly lower in the RPCA group (difference -12; 95% CI -22 to -1.7).

The AUC for pain intensity score was significantly higher in the RPCA group, both in the whole group as in the subgroup of women who actually received analgesia (difference 7.0; 95% CI 1.2 to 13; difference 12; 95% CI 2.1 to 22 respectively)(Table 2).

The satisfaction with pain relief score judged by the women postpartum did not differ between the groups (Table S1). The interval between request for pain relief and the start of analgesia was shorter in the RPCA group compared to the EA group (P = 0.001). Desaturation (<92%) was noted more often in the RPCA group 48/94, compared to the EA group 20/76 (RR 1.2; 95% CI 0.84 to 1.7). Temperature >38°C was registered in 9/94 women in the RPCA group (6/9 after switch to EA) and 6/76 women in the EA group (RR 1.2; 95% CI 0.5 to 3.3). Labour characteristics and maternal and neonatal outcomes were comparable in both groups (Table 3). There were no serious adverse events.

We performed a preplanned subgroup analysis for nulliparous and multiparous women, although interaction was not statistically significant (P = 0.34). In nulliparous women, we observed lower satisfaction with pain relief in women who received analgesia in the RPCA group compared to the EA group (difference -10; 95% CI -21 to 0.58). The AUC for pain intensity for nulliparous women was significantly higher in the RPCA group compared to the EA group (difference 8.7; CI 95% 1.0 to 16). For nulliparous women the duration between request pain relief and start analgesia was shorter in the RPCA group compared to the EA group (P = 0.005).

Table 3. Labour characteristics intention to treat

	RPCA *n* = 203	Epidural *n* = 206	RR (95% CI)	*P*-value
Gestational age at delivery (weeks), median (IQR)	40.3 (39.6-41.0)	40.4 (39.4-41.0)	-- 0.97	0.97
Antepartum referral secondary care	49 (24%)	39 (19%)	1.3 (0.88 to 1.9)	0.20
Indication delivery secondary care	128 (63%)	129 (63%)	1.0 (0.87 to 1.2)	0.93
Nulliparous	103 (75%)	108 (74%)	1.0 (0.88 to 1.2)	0.90
Multiparous	25 (39%)	21 (35%)	1.1 (0.69 to 1.7)	0.69
Spontaneous onset of labour	165 (81%)	168 (82%)	1.0 (0.91 to 1.1)	0.94
Dilatation at request pain relief (cm), median (IQR)	4 (3-5.5)	4 (3-6)	0.31	0.31
Time from request to start analgesia (minutes), median (IQR)	40 (23-60)	58 (34-86)	0.001	0.001
Duration of analgesia (till start pushing) (minutes), median (IQR)	261 (132-414)	295 (203-394)	0.50	0.50
Duration second stage of labour (minutes), median (IQR)	33 (13-76)	34 (14-68)	1.0	1.0
Side effects: *Temperature >38^{o}C	9/94 (10%)	6/76 (8%)	1.2 (0.5 to 3.3)	0.70
Missing	*22 (23%)*	*14 (18%)*		
Saturation < 95%,	55/94 (59%)	25/76 (33%)	1.7 (1.2 to 2.4)	0.002
Missing	*3 (3%)*	*7 (9%)*		
Saturation < 92%	48/94 (51%)	20/76 (26%)	1.2 (0.84 to 1.7)	0.30
Missing	*3 (3%)*	*7 (9%)*		
Post spinal headache	1/94 (1%)	1/76 (1%)	0.81 (0.05 to 12)	1.0
Missing	*45 (48%)*	*9 (12%)*		
Mode of delivery				
Spontaneous	166 (82%)	164 (80%)	1.0 (0.93 to 1.1)	0.58
Vaginal operative	16 (8%)	20 (10%)	0.81 (0.43 to 1.5)	0.51
Caesarean section	21 (10%)	22 (11%)	1.0 (0.55 to 1.7)	0.91
Postpartum haemorrhage (≥1000ml)	18 (9%)	10 (5%)	1.8 (0.86 to 3.9)	0.11
Apgar score <7 at 5 minutes	5 (3%)	1 (<1%)	5.1 (0.60 to 43)	0.12

IQR: interquartile range; *For women who did receive pain relief

Among multiparous women the AUC for satisfaction with pain relief observed in the trial were higher in the RPCA group compared to the EA group although this was not significant (difference 4.7; CI 95% -0.20 to 9.7)(see Tables S2, S3, S4). The per protocol analysis showed similar results to those for the intention-to-treat analysis (see Table S5).

DISCUSSION

Main findings

The results of this study show that we cannot demonstrate that satisfaction with pain relief during labour with RPCA is equivalent to EA in low-risk labouring women. Among women who actually received analgesia scores for satisfaction with pain relief are significantly lower in the RPCA group compared to the EA group.

Strengths and limitations

We studied two methods of analgesia in a large sample of low-risk women. The main strength of this study is that pain satisfaction scores were measured over the whole period of active labour and expressed as AUC unlike most previous studies in which satisfaction was measured 1 hour or maximum of 3 hours after start analgesia.

So far, there is no evidence that measuring scores throughout labour results in a different outcome than measuring an overall score at the end of labour or weeks after it. Our study provides an opportunity to compare the results of measuring satisfaction with pain relief at different moments. Also, we used satisfaction with pain relief as primary outcome, which is most relevant.

Our study also has weaknesses. We did not collect data regarding smoking or other recreational drugs. Another weakness are the missing data for the primary outcome. Missing data could be explained by the fact that hourly scoring to women in labour was a challenge, and not part of routine care. The groups with complete and incomplete data were comparable on baseline characteristics. We decided to use the AUC for the primary outcome, as this is a time-weighted measure and therefore a good overall measurement of satisfaction with pain relief and pain intensity scores. The AUC for pain scores integrates quantity and severity of pain in one outcome measure. Consequently, women with the same value of the AUC might have had different underlying pain sensations. For example, 1 hour of grade 10 unbearable pain gives the total overall score as 3 hours of grade three to four mild pain. However, this pain will most probably be perceived differently. Also, the AUC scores are weighted the same when calculating, but this may or may not be the case. Different satisfaction scores at different points have not been examined in our study.

We opted to use imputation to correct for the missing values, assuming that scores for satisfaction with pain relief were missing at random. In the intention-to-treat analysis we used multiple imputation to adjust for the missing scores. The AUCs after imputation for satisfaction with pain relief and pain intensity were comparable with the AUC without imputation, confirming that our results are a realistic reproduction of the whole group.

Pain relief was administered over a longer period of time in the epidural group compared to the RPCA group. This longer duration influences the AUC with a higher total satisfaction over a longer period of time. However, as the AUC per hour as well as the mean satisfaction score on

specific time-points was significantly worse in the RPCA group, we believe that the superiority of EA was not due to this time effect.

There was a non-compliance of 12% in the RPCA group versus 18% in the EA group. Both preference and prior belief in either RPCA or EA of doctors and women may have influenced the strategy of pain relief used because it was not possible to blind the study. Indeed, some doctors advised women to get EA instead of RPCA. It might have happened that women participated in our study to have the possibility of RPCA during labour because RPCA was only available in the context of our study. Our randomised design, however, makes the baseline profile of two groups of women likely to be similar. Differences in pain perception are therefore due to the actual effectiveness of the treatments, as well as the knowledge of women of to which group they were allocated. The fact that women knew that they were allocated to the RPCA group or the EA group might have influenced their psychological-behaviour. For example if women had a preference for the trial arm they were not allocated to, they would probably have tried harder to cope labour pain without any form of labour analgesia. The pain experienced in labour is effected by psychological factors (3).

The high rate of women (48% RPCA group; 51% EA group) included in our study who did not request for pain relief during labour was due to the trial design. We randomised women antenatally to mimic true clinical scenarios, in which women know which analgesia they would receive if requested. We wanted to evaluate a strategy of EA versus a strategy of RPCA that included not only the effectiveness of the treatments, but also evaluating the decision for analgesia and the effect of it.

The results might not be generalizable to a population where everyone requests pain relief, as the women who actually requested pain relief could be a selection. Our strategy results in a primary outcome influenced by “satisfaction with labour pain” for women without pain relief and “satisfaction with subsequent pain relief” for women receiving analgesia. Both terms are a measure of the acceptability of labour pain but at the same time they may not be interchangeable. Besides, the influence of women who did request, but did not receive pain relief is also present in both groups. Our study mimics the reality. Not receiving analgesia despite a request for it is a part of daily practice in obstetrics in The Netherlands.

The distribution of scores, both pain satisfaction scores and pain intensity scores, was narrow. The only differences in the mean scores between the groups were the scores during analgesia, for both pain satisfaction score and pain intensity score. This is comparable with the AUC outcomes. In the single case that there was only one score registered, for example due to a fast delivery, this score was taken as the mean. The difference in AUC between nulliparous women and multiparous women is most likely the result of the longer interval for delivery for nulliparous compared with multiparous women.

Interpretation

The outcome of our study is comparable to our previous RAVEL study (16). In both studies satisfaction with pain relief during the total period of labour was comparable between the RPCA group and the EA group. Both studies showed significantly lower satisfaction with pain relief in the RPCA group after the start of analgesia and significantly higher pain intensity scores in the RPCA group during active labour.

The longer interval between the request for pain relief and the start of analgesia in the RPCA group of our study compared with the RPCA group of our previous RAVEL study could be explained by referral from midwife-led primary care to obstetrician-led secondary care in the case of a request for pain relief.

In contrast to our study, Volmanen et al. and Douma et al. measured comparable satisfaction with pain between RPCA and EA (10,11). These studies probably did not find a difference either because of a smaller sample size or because pain intensity scores were assessed maximum 3 hours after start analgesia whereas pain intensity scores usually increase 2 hours after the start of RPCA (11).

Comparable to previous authors, we did not find differences in satisfaction with pain relief when asked in retrospect (9,11–13). Our trial confirms previous studies in the superiority of EA over RPCA for pain intensity measured during active labour (3).

As it is generally accepted that analgesia during labour should be available, alternatives are needed when EA is not, immediately, available, contraindicated or not preferred by the woman.

The preference of some women for RPCA, although randomised for EA, indicates that women consider other favourable factors more important than the effectiveness of pain relief.

The percentage of women who requested pain relief was comparable between both groups. More women in the RPCA group received analgesia, because RPCA could be started without an anaesthetist. Besides, RPCA was provided even at the end of the first stage of labour whereas EA was not provided to women late in the first stage of labour, which is a common policy in some countries, including the Netherlands. Hence, women in need of pain relief might choose for RPCA when the expected time to delivery is short.

Although there was no significant interaction between parity and pain relief method we observed a higher satisfaction with pain relief in the RPCA subgroup of multiparous women compared to the EA group, which could be clinically relevant. This could be explained by the shorter use of analgesia in this group which is favourable for RPCA. In previous studies pain intensity scores during RPCA increased over time whereas pain scores during EA were sustained over time (9,11). Besides, most of the multiparous women who asked for pain relief but did not receive pain relief belonged to the EA group (10/60), compared to 3/65 in the RPCA subgroup. In our opinion, especially for multiparous women RPCA is an attractive option for analgesia with acceptable satisfaction scores. These women will usually take advantage of a fast delivery combined with rapid availability and a short use of pain relief.

The incidence of desaturation in our study confirms the well-known risk of respiratory complications during RPCA (3–5,16,19). Measuring of the respiratory rate was, at least during our study, not a standard procedure in all the hospitals. Despite the frequently monitored desaturation we did not observe respiratory depression or serious complications in either group. RPCA should only be used with careful monitoring for respiratory complications and in the attendance of trained health care providers.

The cross-over from RPCA to EA was comparable to previous studies (16,19). In clinical practice the dilatation at request of pain relief is usually taken into account when decision for a strategy of analgesia is made, possibly leading to lower cross-over rates. Nulliparous women who were dilated ≤ 4 cm are at risk for insufficient analgesia with RPCA. Caregivers should take this into account when counselling for analgesia during labour.

The result of our study facilitates shared decision-making about analgesia during labour. Pregnant women should be fully informed about the options for analgesia including the effects, limitations and risks of these options. RPCA should particularly be discussed in multiparous women.

CONCLUSION

When comparing a strategy for RPCA with EA in women at low risk for complications, equivalence could not be demonstrated with respect to satisfaction with pain relief assessed during the total time of labour. However, once applied, satisfaction with pain relief was higher in women who received EA. Since RPCA is in many settings more readily available than EA, it can be an alternative for pain relief during labour.

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ADDITIONAL FILES

Table S1. Secondary outcome

Mean (SD) satisfaction with pain relief and pain intensity score.

		RPCA		Epidural		
SATISFACTION WITH PAIN RELIEF	**Number**	**Mean(SD)**	**Number**	**Mean(SD)**	**Difference (95% CI)**	***P*-value**
During active labour	171/203	5.4 (1.8)	144/206	5.5 (2.0)	-0.35 (-0.45 to 0.38)	0.87
At request pain relief	62/105	4.2 (2.1)	50/101	4.1 (2.7)	0.08 (-0.84 to 1.0)	0.86
During analgesia	47/94	5.1 (2.1)	32/76	6.4 (2.1)	-1.3 (-2.2 to -0.32)	0.01
Overall 2 hours postpartum	181/203	6.1 (2.1)	167/206	6.0 (2.4)	0.03 (-0.45 to 0.51)	0.90
Overall 6 weeks postpartum	201/203	6.0 (2.3)	192/206	5.8 (2.4)	0.19 (-0.28 to 0.67)	0.43
PAIN INTENSITY SCORE						
During active labour	175/203	6.8 (1.5)	148/206	6.6 (1.8)	0.24 (-0.12 to 0.61)	0.19
At request pain relief	63/105	7.7 (1.7)	49/101	7.7 (2.0)	-0.03 (-0.73 to 0.66)	0.93
During analgesia	48/94	6.5 (1.7)	31/76	4.1 (2.0)	2.4 (1.6 to 3.2)	<0.01
Overall 6 weeks postpartum	201/203	7.1 (1.8)	192/206	7.1 (1.8)	0.03 (-0.32 to 0.39)	0.86

RPCA: remifentanil patient controlled analgesia; SD: standard deviation

Table S2. Subgroup analysis nulliparous women

Mean area under the curve for satisfaction with pain relief and pain intensity scores during active labour and after start analgesia.

Mean (SD) satisfaction with pain relief and pain intensity score.

	RPCA ***n* = 138**		**Epidural** ***n* = 146**		**Difference (95% CI)**	***P*-value**
Request pain relief	86/138 (62%)		77/146 (53%)		1.2 (0.97 to 1.4)	0.10
Received analgesia	78/138 (57%)		62/146 (43%)		1.3 (1.1 to 1.7)	0.02
Mean area under curve	**AUC**		**AUC**			
Satisfaction with pain relief during active labour	37		38		-1.3 (-9.5 to 6.8)	
Satisfaction with pain relief during analgesia	26		36		-10 (-21 to 0.58)	
Pain intensity score during active labour	48		39		8.7 (1.0 to 16)	
Pain intensity score during analgesia	33		18		14 (3.1 to 25)	
Overall postpartum	**N Mean (SD)**		**N**	**Mean (SD)**	**Difference (95% CI)**	***P*-value**
Satisfaction with pain relief 2 hours postpartum, mean (SD)	123/138	6.0 (2.1)	118/146	6.0 (2.3)	-0.03 (-0.59 to 0.52)	0.91
Satisfaction with pain relief 6 weeks postpartum, mean (SD)	137/138	5.9 (2.4)	134/146	5.6 (2.5)	0.32 (-0.26 to 0.90)	0.27
Pain intensity score 6 weeks postpartum**,** mean (SD)	137/138	7.2 (1.9)	134/146	7.1 (1.7)	0.08 (-0.35 to 0.51)	0.72

RPCA: remifentanil patient controlled analgesia; AUC: area under the curve; SD: standard deviation

Table S3. Subgroup analysis multiparous women

Mean area under the curve for satisfaction with pain relief and pain intensity scores during active labour and after start analgesia. Mean (SD) satisfaction with pain relief and pain intensity score.

	RPCA N = 138		Epidural N = 146	Difference (95% CI)	*P*-value
Request pain relief	19/65 (29%)		24/60 (40%)	0.73 (0.45 to 1.2)	0.21
Received analgesia	16/65 (25%)		14/60 (23%)	1.1 (0.56 to 2.0)	0.87
Mean area under curve	**AUC**		**AUC**		
Satisfaction with pain relief during active labour	17		12	4.7 (-0.20 to 9.7)	
Satisfaction with pain relief during analgesia	7		13	-5.6 (-14.0 to 12.9)	
Pain intensity score during active labour	20		17	3.3 (-2.5 to 9.2)	
Pain intensity score during analgesia	11		7	4.1 (-11 to 19)	
Overall postpartum	**N Mean (SD)**	**N**	**Mean (SD)**	**Difference (95% CI)**	***P*-value**
Satisfaction with pain relief 2 hours postpartum, mean (SD)	58/65 6.3 (2.0)	49/60	6.2 (2.7)	0.15 (-0.79 to 1.1)	0.76
Satisfaction with pain relief 6 weeks postpartum, mean (SD)	64/65 6.3 (2.3)	58/60	6.4 (2.3)	-0.13 (-0.95 to 0.68)	0.75
Pain intensity score 6 weeks postpartum, mean (SD)	64/65 7.0 (1.6)	58/60	7.0 (1.9)	-0.07 (-0.7 to 0.57)	0.84

RPCA: remifentanil patient controlled analgesia; AUC: area under the curve; SD: standard deviation

Table S4. Labour characteristics nulliparous and multiparous women

	RPCA		Epidural		
	Number	**Median (IQR)**	**Number**	**Median (IQR)**	***P*-value**
Dilatation at request pain relief (cm)					
Nulliparous	78/78	4 (3-5)	62/62	4 (3-6)	0.32
Multiparous	16/16	4 (3-7)	14/14	4.5 (3-6)	0.95
Time from request to start analgesia (minutes)					
Nulliparous	74/78	40 (22-67)	60/62	54 (35-90)	0.005
Multiparous	15/16	38 (25-58)	14/14	64 (19-79)	0.10
Duration of analgesia (minutes)					
Nulliparous	63/78	322 (149-430)	51/62	335 (256-447)	0.23
Multiparous	13/16	93 (53-185)	14/14	60 (22-200)	0.30
Duration second stage of labour (minutes)					
Nulliparous	123/138	64 (33-105)	126/146	84 (38-115)	0.16
Multiparous	62/65	11 (6-20)	59/60	12 (7-23)	0.55

RPCA: remifentanil patient controlled analgesia; IQR: interquartile range

Table S5. Per protocol analysis

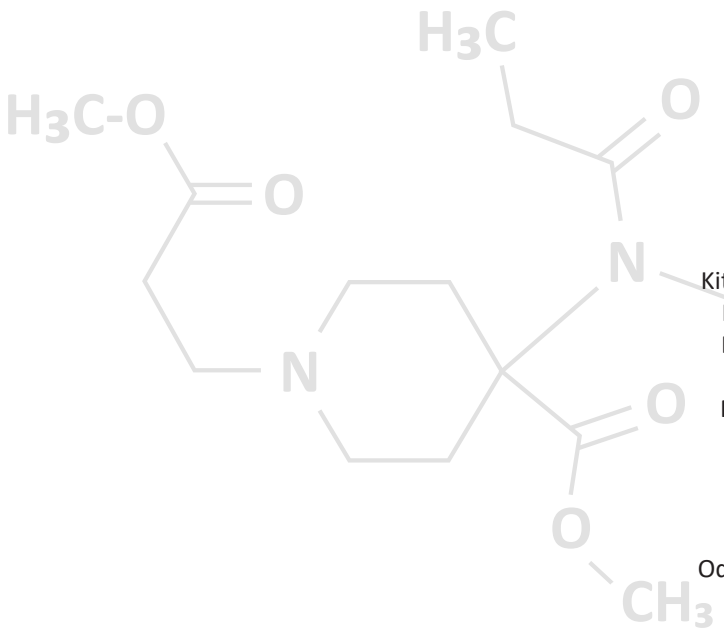
Mean area under the curve for satisfaction with pain relief and pain intensity scores during active labour and after start analgesia.

Per protocol analysis *Missing values not imputed*	**RPCA** **N = 95**	**Epidural** **N = 72**	
Mean area under the curve	**AUC**	**AUC**	**Risk Difference (95%CI)**
Satisfaction with pain relief			
During active labour	42	56	-14 (-25 to 2.3)
During analgesia	23	35	-12 (-22 to -1.5)
Pain intensity score			
During active labour	54	50	3.5 (-7.2 to 14.3)
During analgesia	29	17	12.2 (1.9 to 22.5)

RPCA: remifentanil patient controlled analgesia; AUC: area under the curve

CHAPTER 3

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.

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, while Douma and colleagues recorded pain relief scores as a secondary outcome in a study powered to investigate difference in pain scores (5,6). 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), 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 (8).

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 specially 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. After birth, women were asked to rate 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^{o}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 cardiopulmonaryresuscitation, 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 and converted those from a five point to an 11 point scale (5). 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).

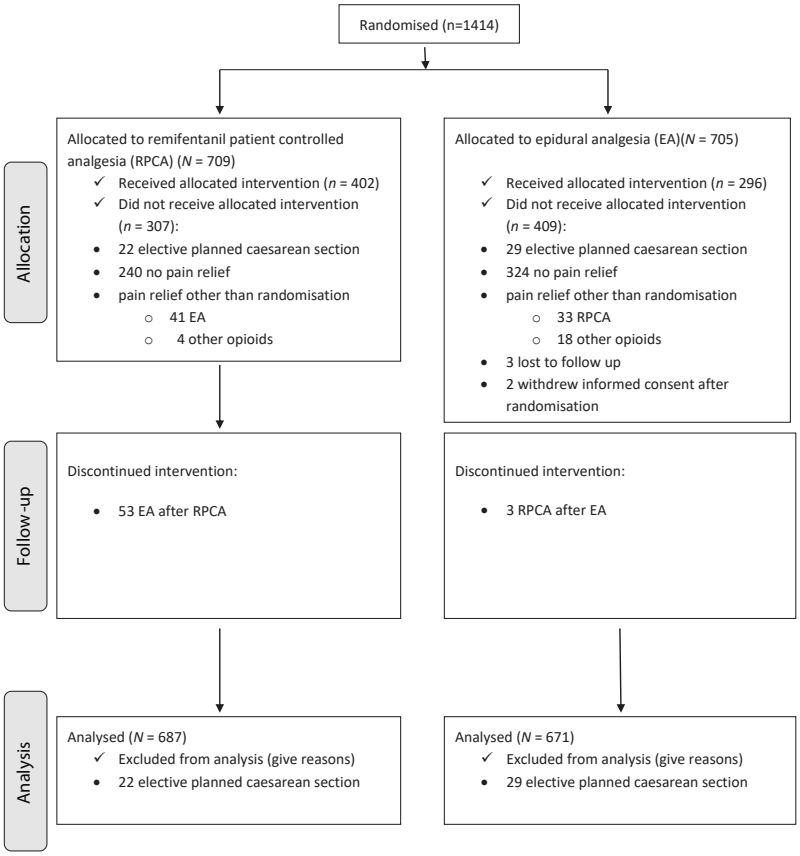

Figure 1. Randomisation and flow of pregnant women allocated to patient controlled remifentanil or epidural analgesia in labour

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. Forty five 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 µg. 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. Fifty one women 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	**Randomised to remifentanil, received epidural analgesia**
	n = 33	***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.

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).

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.

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).

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).

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	—	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.

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 (median duration 25, interquartile range 11-51 minutes) compared with epidural analgesia (34, 15-60; 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 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.

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 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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CHAPTER 4

Pharmacological pain relief and fear of childbirth in low risk women; secondary analysis of the RAVEL study.

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ABSTRACT

Background Fear of childbirth may reduce the womens' pain tolerance during labour and may have impact on the mother-infant interaction. We aimed to assess (1) the association between fear of childbirth antepartum and subsequent request for pharmacological pain relief, and (2) the association between the used method of pain relief and experienced fear of childbirth as reported postpartum in low risk labouring women.

Methods Secondary analysis of the RAVEL study, a randomised controlled trial comparing remifentanil patient controlled analgesia (PCA) and epidural analgesia to relieve labour pain. The RAVEL study included 409 pregnant women at low risk for obstetric complications at 18 midwifery practices and six hospitals in The Netherlands. We measured fear of childbirth antepartum and experienced fear of childbirth reported postpartum, using the Wijma Delivery Expectancy/Experience Questionnaire.

Results Women with fear of childbirth antepartum more frequently requested pain relief compared to women without fear of childbirth antepartum, but this association did not reach statistical significance (adjusted odds ratio (aOR2.0; 95% confidence interval (CI) 0.8-4.6). Women who received epidural analgesia more frequently reported fear of childbirth postpartum compared to women who did not receive epidural analgesia (aOR3.5; CI 1.5-8.2), while the association between remifentanil-PCA and fear of childbirth postpartum was not statistically significant (aOR1.7; CI 0.7-4.3).

Conclusions Women with fear of childbirth antepartum more frequently requested pain relief compared to women without fear of childbirth antepartum, but this association was not statistically significant. Women who received pharmacological pain relief more frequently reported that they had experienced fear of childbirth during labour compared to women who did not receive pain relief. Based on our data epidural analgesia with continuous infusion does not seem to be preferable over remifentanil-PCA as method of pain relief when considering fear of childbirth postpartum.

BACKGROUND

Labour pain is considered as severe pain (1). Womens' experiences of labour pain vary and are influenced by the physiological and psychological processes of birth and the extent to which women perceive pain (2). Fear of childbirth, meaning pregnancy and childbirth related fear and anxiety, can lead to an increased pain perception (3,4). Due to its possible impact on both the mother and on the mother-infant interaction fear of childbirth has gained growing attention (4–6). One can distinguish fear of childbirth antepartum –measured during pregnancy– from fear of childbirth postpartum, which is fear experienced during labour and measured after giving birth (7).

Previous studies have shown that women with fear of childbirth had reduced pain tolerance (4,8). Adams et al. found that women with fear of childbirth more often requested epidural analgesia during labour than women without fear of childbirth (45% vs 27%, p<0.001)(9). Saisto et al. found that 15% of the women with fear of childbirth postpartum, mentioned experienced frightening pain as principal cause of fear (10).

Pharmacological methods of pain relief are widely used during labour (2). There is variation in the methods of pain relief and in the percentage of women using pain relief (2,11–13). Pharmacological pain relief reduces the pain experienced during labour (2,14,15). However, childbirth satisfaction is not only influenced by pain and pain relief but also by other factors such as the attitude of the caregivers and involvement of the woman in decision making during labour (16). There is a lack of robust data assessing the experiences of women who receive and who do not receive analgesia and their childbirth experience or well-being, including fear of childbirth.

In The Netherlands women at low risk for obstetric complications start labour in primary midwife-led care. In case of a request for pharmacological pain relief –with the exception of Entonox- women will be referred to hospital-based obstetric-led care and the primary care midwife is no longer involved in providing care. A referral during labour -for pharmacological pain relief or other medical reasons- could be influenced by fear of childbirth antepartum or could influence experienced fear of childbirth reported by women postpartum (5,8–10,17).

Both the relation between fear of childbirth antepartum and request for pain relief as well as administering pharmacological pain relief and experienced fear of childbirth reported postpartum, have rarely been studied in a low risk population. More knowledge about this topic could be used for counselling women for decisions regarding the use of pharmacological pain relief, the type of pain relief and the preferred place of birth.

The aim of our study was to assess, in low risk labouring women, the association between fear of childbirth antepartum and request for pharmacological pain relief. Furthermore, we assessed the association between the used method of pain relief and experienced fear of childbirth as reported postpartum.

METHODS

Design

We studied the association between on the one hand fear of childbirth antepartum and a request for pharmacological pain relief (either remifentanil patient controlled analgesia (PCA) or epidural analgesia), and on the other hand the association between the method of pharmacological pain relief and fear of childbirth -experienced during labour- reported postpartum in women who participated in the RAVEL trial (NTR3687). This was a randomised equivalence trial among 409 low risk pregnant women comparing two pharmacological pain relief methods – remifentanil-PCA and epidural analgesia– in case of a request for pain relief during labour (14). In this trial satisfaction with pain relief and pain scores were compared over the total duration of labour among low risk women randomised for remifentanil-PCA or epidural analgesia. Maternal satisfaction with labour pain scores and pain intensity scores were assessed hourly from the start of active labour until the second stage of labour in all participating women. Women receiving remifentanil-PCA were less satisfied with their pain relief than women using epidural analgesia (14).

The RAVEL study was approved by the ethics committee of the University Medical Centre Leiden and the boards of the six participating hospitals (ref. no. P10.240; 26 July 2012). Written informed consent was obtained of all participants and women younger than 18 years were not eligible.

The participants filled out the Wijma Delivery Expectancy/Experience Questionnaire antepartum version (W-DEQ A) and gave their informed consent for the researchers to extract data from the maternity care record. These data were obtained by the participant's primary care midwife. Six weeks postpartum participants received a reminder e-mail from the researchers to completethe W-DEQ post-partum version (W-DEQ B). Completed questionnaires were sent to the researchers by post.

Definition and measurements of the outcome

Women were asked to complete the W-DEQ A during the third trimester of pregnancy and the W-DEQ B at six weeks postpartum, consistent with other studies. The W-DEQ A was developed to measure women's feelings and fear before labour by means of the woman's cognitive appraisal regarding the labour process. Similarly, the W-DEQ B was developed to measure, in retrospect, feelings and fear that women had experienced during childbirth. W-DEQ is a self-assessment scale -containing 33 items in both questionnaires- regarding childbirth (questions like, 'How do you think you will feel in general during labour and delivery?' in W-DEQ A or 'How did you feel in general during labour and delivery?' in W-DEQ B: extremely weak/not at all weak; extreme panic/not at all panicked; extreme trust/no trust at all). Answers are given on a six-point Likert scale ranging from 'not at all' (0) to 'extremely' (5), yielding a minimum score of 0 and a maximum score of 165, with higher scores reflecting a greater degree of fear

of childbirth. According to the literature we classified the W-DEQ score in three categories (7,9,18,19). A score <85 presenting women with low to moderate fear of childbirth; a score between 85 and less than 100 indicating women with an intense fear of childbirth, influencing the woman's well-being, and women with a score of 100 or higher were defined as having a very intense, fobic fear. The internal consistency for both versions of the W-DEQ is shown to be good (Cronbach's alpha=0.93)(7).

Definition and measurements of potentially confounding variables.

We selected potentially confounding variables associated with fear of childbirth on the basis of the literature and one variable (obstetric complication) was added from clinical experience. Pre-existing psychological conditions – mainly anxiety and depression – could have an impact on the expectations of labour and could confound the relation between fear of childbirth and request for pain relief (7,18–21). To identify pre-existing psychological conditions, we measured anxiety and depression by using the Hospital Anxiety Depression Scale (HADS). Women were asked to complete the HADS questionnaire simultaneously with the W-DEQ questionnaire at both time points. The HADS is a questionnaire containing a 7-item anxiety scale and a 7-item depression scale, both of which have scores ranging from 0 to 21. The HADS is designed to measure depression and anxiety disorders among patients in a non-psychiatric clinic and is considered to be a reliable and efficient questionnaire (22,23). A cut off score of ≥11 points on each scale was used to define the existence of anxiety and/or depression (23).

Other potentially confounding variables for either fear of childbirth antepartum and/or postpartum were young maternal age (18), low education level (18), previous first trimester loss (23), parity (5,9,18,23), (previous) emergency caesarean section or operative vaginal delivery (5,9,10,17), use of epidural analgesia during labour (9,10), duration of labour (defined as the time from start active labour to birth)(9,10), induction/augmentation of labour (8,10,17).

Partly from the literature, combined with clinical experience, we added obstetric complication as a potential confounder. In the RAVEL trial obstetric complications were defined as post spinal headache, postpartum haemorrhage (≥1000 ml in the 24 hours after delivery or administration of blood products), uterine rupture, eclampsia, amniotic fluid embolism, myocardial infarction or admission to ICU) and/or neonatal admission to intensive care (10). Due to, firstly the small study population and secondly, the low risk population in which we expected low rates of obstetric complications and interventions, we decided to combine these into one variable 'obstetric intervention/complication', with interventions including induction/augmentation of labour, assisted vaginal delivery, emergency caesarean section and obstetric complications into one variable. Additional file 1 shows the frequencies of these variables. As our study population consisted of women with a low obstetrical risk, women with a previous caesarean were excluded. For the second research question we added fear of childbirth antepartum as a potential confounder (17,20).

Analysis

To determine whether women who completed the W-DEQ questionnaires were representative for the total study population, we compared the baseline characteristics of women who completed the antepartum W-DEQ questionnaires with those of women who did not. The same was done for the postpartum W-DEQ questionnaires. To do so, we used the chi-square test, Mann-Whitney U test and the Student's *t*-test. Prior to the analysis, the W-DEQ and HADS scores were examined for missing items. For the W-DEQ a maximum of two missing items was allowed, and missing items were assigned the mean score of all other items for that specific participant's scale.

Multiple logistic regression analysis was used to determine whether there was an association between fear of childbirth antepartum and a request for pain relief (research question 1). All potentially confounding factors were included in the multiple logistic regression analysis, with a request for pain relief as the dependent variable.

To study whether the method of pain relief, remifentanil-PCA or epidural analgesia (randomly allocated), was associated with fear of childbirth reported postpartum we used multiple logistic regression analyses (research question 2). Because of the relatively small group of women with fear of childbirth reported postpartum we had to determine the most relevant potential confounders for the multiple regression analysis. We did a pre-selection with univariable logistic regression analysis. Variables with a p-value ≤ 0.2 were included in a stepwise multivariable logistic regression analysis using a backward selection method to determine factors most strongly associated with fear of childbirth reported postpartum (24). All tests of significance were two-sided, with a p value ≤ 0.05 indicating statistical significance. Data were analyzed using SPSS (version 24; SPSS Inc., Chicago, IL).

RESULTS

Of the 409 women participating in the RAVEL trial, 374 (91%) women completed the W-DEQ questionnaire antepartum and 315 (77%) completed the W-DEQ questionnaire postpartum. Figures 1A&B show the flow charts for both measures. The baseline characteristics of women who completed the W-DEQ questionnaire antepartum and women who did not were comparable. Of women who completed the W-DEQ questionnaires postpartum and women who did not, the baseline characteristics were comparable, except for the variables random allocation, ethnic origin and education level. More women randomised for remifentanil-PCA, more Western women and more women with a higher education level completed the W-DEQ questionnaires postpartum (p=0.003, p=0.008 and p=0.004 respectively). Of the 53 women with a low education level 12 (23%) experienced (very) intense fear of childbirth postpartum compared to 24 (9%) of the 253 women with a high education level. Table 1 shows the baseline

characteristics of all the women who participated in the RAVEL study and of the women who completed the W-DEQ A and the W-DEQ B.

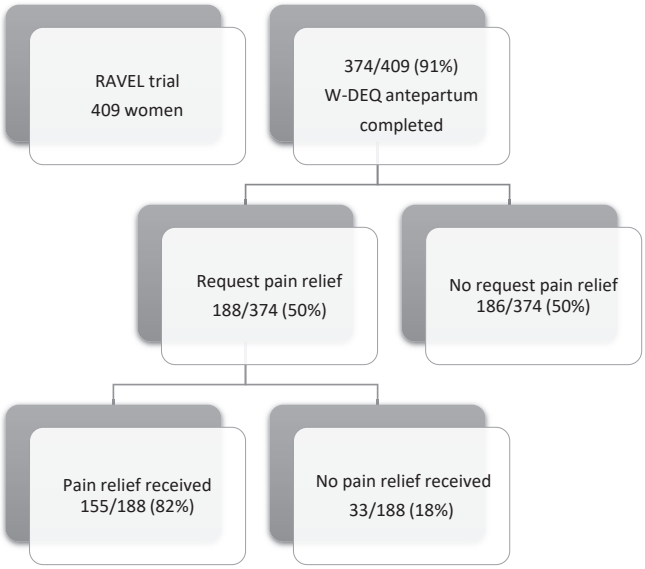

Figure 1A. Flowchart of women in the RAVEL trial who did complete the W-DEQ A (antepartum)

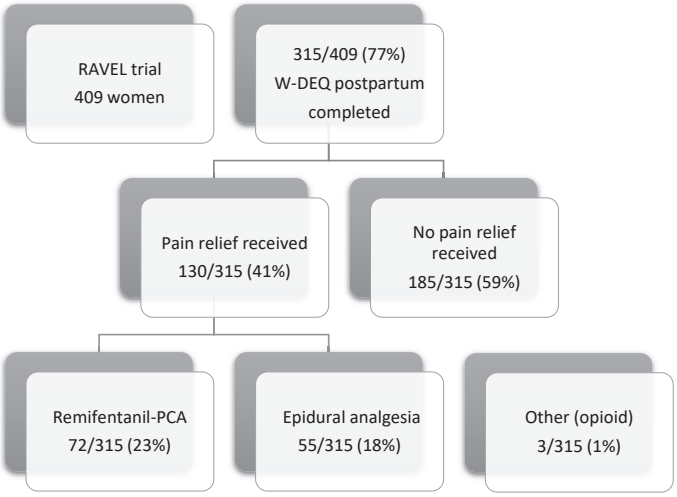

Figure 1B. Flowchart of women in the RAVEL trial who did complete the W-DEQ B (postpartum)

Table 1. Baseline characteristics at randomisation of women who participated in the RAVEL study and who did complete the W-DEQ antepartum and/or the W-DEQ postpartum

	W-DEQ antepartum (n= 374) n (%)	W-DEQ postpartum (n=315) n (%)	RAVEL study n=409 (%)
Gestational age (weeks), median [IQR]	36 [34-38]	36 [34-38]	36 [34-38]
Maternal age (years), mean (SD)	32 (4.1)	32 (4.0)	32 (4.1)
Randomisation allocation RAVEL trial			
Remifentanil-PCA	186 (50)	169 (54)	203 (50)
Epidural analgesia	188 (50)	146 (46)	206 (50)
Ethnic origin			
Western	342 (91)	293 (93)	372 (91)
Non Western	32 (9)	22 (7)	37 (9)
Education			
≤ Low-medium professional school	75 (20)	53 (17)	81 (20)
≥ Higher professional school	288 (77)	253 (80)	314 (77)
Unknown	11 (3)	9 (3)	14 (3)
Body mass index (kg/m^2) mean (SD)	23 (3.4)	23 (3.4)	23 (3.4)
Parity			
0	262 (70)	222 (71)	284 (69)
≥1	112 (30)	93 (30)	125 (31)
Pain relief requested			
No	186 (50)	157 (50)	203 (50)
Yes	188 (50)	158 (50)	206 (50)
Pain relief received			
No	219 (59)	185 (59)	239 (58)
Yes	155 (41)	130 (41)	170 (42)
Remifentanil-PCA	*80 (21)*	*72 (23)*	*94 (23)*
Epidural analgesia	*72 (19)*	*55 (18)*	*76 (19)*
Other (opioid)	*3 (1)*	*3 (1)*	*3 (1)*
W-DEQ score (level of fear of childbirth)			
<85 (low-medium fear of childbirth)	342 (91)	278 (88)	-
≥85 and <100 (intense fear of childbirth)	30 (8)	26 (8)	-
≥100 (very intense/fobic fear of childbirth)	2 (1)	11 (4)	-

IQR: interquartile range; SD: standard deviation

Association between fear of childbirth antepartum and request for pain relief

The mean W-DEQ sum score antepartum was 63 (SD 16). Thirty women (30/374, 8%) had an intense fear of childbirth, while two women (<1%) had very intense fear of childbirth. As only two women had a score of 100 or higher, we decided to combine the women with intense and very intense fear of childbirth in one group. Of the 374 women, 188 (50%) requested pain relief (Figure 1A). No differences were found between the characteristics of women who requested pharmacological pain relief and women who did not, except for the variable parity. The group of women with a request for pain relief consist of more nulliparous women compared to group without a request for pain relief (<0.001)(Additional file 2). We did find an adjusted odds ratio of 2.0 (CI 0.8-4.6) between fear of childbirth antepartum and request for pain relief after

adjusting for parity, maternal age, education level, previous first trimester loss, antepartum HADS score and previous vaginal instrumental delivery but this association was not statistically significant (Table 2).

Table 2. Association between antepartum fear of childbirth and request for pharmacological pain relief

	Request pain relief, n=188 n (%)	No request pain relief, n=186 n (%)	OR (95% CI)	Adjusted OR (95% CI)
Fear of childbirth antepartum*			1.7 (0.8-3.6)	2.0 (0.8-4.6)
Low-medium fear of childbirth (<85) [ref]	168 (89)	174 (94)		
(Very) intense fear of childbirth (≥85)	20 (11)	12 (7)		

*Adjusted for parity; maternal age; education level; previous first trimester loss; antepartum HADS score; previous vaginal instrumental delivery.

Association between method of pain relief and fear of childbirth reported postpartum

The mean W-DEQ sum score postpartum was 55 (SD 24), 26 of the 315 (8%) women had experienced intense fear of childbirth and 11 (4%) women had experienced very intense fear of childbirth. We decided to combine women with intense and very intense fear of childbirth for the analysis. Of the 315 women, 130 (41%) women received pain relief: 72 (23%) women received remifentanil-PCA, 55 (18%) women received epidural analgesia, 3 (1%) women received another opioid and 185 (59%) women did not receive pain relief (Figure 1B). Of the women who requested pain relief, 28/158 (18%) women did not receive pain relief although requested, mostly due to delivery before analgesia was in place.

In the univariable logistic regression analyses we found the administration of pharmacological pain relief to be associated with fear of childbirth reported postpartum compared to deliveries without pharmacological pain relief (p=0.002). Women who received epidural analgesia, more often reported fear of childbirth postpartum compared to women who did not use pain relief (OR 4.2; CI 1.9-9.6), while the association with remifentanil-PCA was not statistically significant (OR 1.8; CI 0.7-4.3). In the univariable analysis we selected the variables fear of childbirth antepartum, parity, education level, duration of labour and obstetric intervention/complication as they met the criterion p<0.2. A higher level of fear of childbirth antepartum was related to a higher level of fear of childbirth reported postpartum. Nulliparity predicted a higher chance for fear of childbirth reported postpartum than multiparity. A higher education level and a longer duration of labour were predictive for fear of childbirth reported postpartum. Also, the occurrence of an obstetric intervention/complication was predictive for fear of childbirth reported postpartum (Additional file 3).

After multivariable logistic regression analysis using backward selection with the variables parity, maternal age, education level, fear level antepartum, duration of labour and obstetric intervention/complication, the association between receiving pharmacological pain relief and

fear of childbirth reported postpartum remained significant (p=0.02). Women who used epidural analgesia, more often reported fear of childbirth postpartum than women who did not use pain relief (OR 3.5; CI 1.5-8.2), while for remifentanil-PCA this difference was not statistically significant (OR 1.7; CI 0.7-4.3)(Table 3).

Table 3. Association between whether or not pharmacological pain relief was received and fear of childbirth reported postpartum: multivariable analysis

Variable	Fear level reported postpartum low-medium (<85) n=278	Fear level reported postpartum (very) intense (≥85) n=37	Adjusted OR* (95% CI)
Pain relief			
No pain relief [ref]	174 (62%)	14 (38%)	
Remifentanil-PCA	63 (23%)	9 (24%)	1.7 (0.7-4.3)
Epidural analgesia	41 (15%)	14 (38%)	3.5 (1.5-8.2)
Fear of childbirth antepartum			
Low-medium (<85) [ref]	255 (94%)	29 (78%)	3.9 (1.4-10.8)
High (≥85 and <100)	16 (6%)	8 (22%)	
& severe (≥100)			
Missing	7	0	
Education level(professional school)			
≤ Medium [ref]	41 (15%)	12 (33%)	0.4 (0.2-0.9)
≥ Higher	229 (85%)	24 (67%)	
Missing	8	1	

*Adjusted for maternal age; parity; education level; duration of labour; obstetric intervention/complication; fear of childbirth antepartum (W-DEQ A)

DISCUSSION

Main findings

We observed that women with fear of childbirth antepartum more often requested pain relief, although this association did not reach statistical significance. The results of our analyses also suggest that women who received pharmacological pain relief more often reported experienced fear of childbirth postpartum compared to women who did not use pain relief. This association was statistically significant for women who used epidural analgesia with continuous infusion, while it did not reach statistical significance for women who used remifentanil-PCA.

Interpretation

The frequency of fear of childbirth antepartum (8,5%) and fear of childbirth reported postpartum (11,7%) in our study was in accordance with the literature (5,10,17). Comparable with

previous studies, we observed that women with fear of childbirth antepartum were more likely to request pain relief during labour, although our study did not show statistical significance (8,10,25). This might be because of a lack of power in our study. Another explanation could be that our study population consisted of low risk labouring women under the care of a primary care midwife. It is assumed that women receive continuous support of labour during midwife-led care. Previous research showed that continuous support of labour results in less pharmacological pain relief (26,27). Also, one might assume that these healthy women probably have other expectations towards pain and the use of pharmacological pain relief compared to women with a medium to high obstetric risk already under care of an obstetrician. Besides, it is known that there are different reasons for fear of childbirth antepartum, like fear of the unknown, loss of control and labour pain (5). Geissbuehler et al. found fear of labour pain as one of the most frequent reasons for fear of childbirth (27). However, we did not have information about the background of fear of childbirth in our study population.

Our study shows that women who used epidural analgesia with continuous infusion more often report fear of childbirth postpartum compared to women who did not use pharmacological pain relief. We did not find this relation for the use of remifentanil-PCA. Previous studies did not distinguish between the method of pain relief, but usually only reported about epidural analgesia. To our knowledge, there are no studies about the association between remifentanil-PCA and fear of childbirth. Possibly, the effect of remifentanil-PCA at the birth experience towards experienced fear of childbirth is different from the effect of epidural analgesia- a more invasive method of pain relief. Although epidural analgesia gives lower pain scores and a better satisfaction with pain relief, our study suggests that women who received remifentanil-PCA do not report more fear of childbirth postpartum compared to women who used epidural analgesia with continuous infusion (14,15).

Our study population contains mainly Western, highly educated women. In addition, less women with a low education level completed the W-DEQ postpartum compared to women with a high education level. This may have influenced of the results of our study. Fear of childbirth reported postpartum occurred more often in women with a low education level (23%) compared to women with a high education level (9%). This is in accordance with Laursen et al. who found that fear of childbirth is expected to be higher in women with a lower education level (18). Therefore, our results are probably an underestimation of fear of childbirth reported postpartum by low-risk pregnant women which limits the generalisability of our study.

The result that fear of childbirth antepartum is cogent related to fear of childbirth reported postpartum is consistent with previous studies (7,17,20,23). The childbirth experience is more affected by already existing antepartum fear of childbirth than by interventions or complications during labour (20,28). It is shown before that fear of childbirth is associated with obstetric intervention/complications as well as with caesarean section as preferred mode of delivery (5,9). This knowledge makes it important to distinguish fear of childbirth antepartum. Once recognized, women can make an informed choice for treatment of their fear of childbirth in

order to prevent both obstetric intervention/complications and fear of childbirth reported postpartum as well as perinatal costs (28–30).

Strengths and limitations

The main strength of our study is the high response rate for both questionnaires, antepartum (91%) and postpartum (77%). Second, our study population was extracted from the randomised RAVEL trial with many possible confounders for fear of childbirth included in the dataset. We had the opportunity to adjust for most potential confounders. Another strength is that our study distinguishes the applied method of pain relief -instead of pain relief in general- in relation to fear of childbirth reported postpartum.

Our study also has weaknesses. First, the group of women with fear of childbirth reported postpartum is relatively small. This study was a secondary analysis therefore it is possible that we did not find associations because of a lack of statistical power. Second, we combined obstetric interventions and complications into one variable 'obstetric intervention/complication' although the influence of every single variable at the onset of fear of childbirth postpartum could be different. Due to our small study population and the low rates of the interventions and complications it was not possible to use the individual variables in our analysis. Third, although we adjusted for the majority of potential confounding variables residual confounding could exist. Earlier research showed some other possible confounders which could influence fear of childbirth reported postpartum, for instance lack of social support, dissatisfaction with partnership and insufficient support of the caregiver (16,21). Information about these aspects was not available in our dataset, therefore we did not have the possibility to adjust for all potential confounders.

Furthermore, a possible weakness for the extrapolation to practice could be the population of the randomised design of the RAVEL study. The fact that women knew that they were allocated to the remifentanil-PCA group or the epidural analgesia group might have influenced their psychological behaviour. For example, if women had a preference for the trial arm they were not allocated to, they would probably have tried harder to cope with labour pain without any form of labour analgesia. Besides, remifentanil-PCA and epidural analgesia were given on a request for pain relief irrespective of the stage of labour. In contrast to daily practice, when the stage of labour is taken into account to distinguish which method of pain relief will be appropriate. There could have been influence from this randomised design on the outcome measure fear of childbirth reported postpartum, for example depending of the satisfaction with pain relief the woman has experienced. In addition, the number of women who reported fear of childbirth postpartum could have been influenced by women who did not receive pain relief unless a request for it. This could have led to an overvaluation of women with fear of childbirth postpartum in the group of women who did not use pain relief. Lastly, in the RAVEL study epidural analgesia was given with continuous infusion which is associated with a greater need for provider-delivered boluses for breakthrough pain compared to patient controlled epidural

analgesia. It is possible that the quality of analgesia from continuous epidural infusions negatively affected fear of childbirth postpartum (31). To judge on extrapolation to the comparison between epidural-PCA and remifentanil-PCA further research is needed.

CONCLUSION

Women with fear of childbirth antepartum more frequently requested pain relief, but this association did not reach statistical significance. Women who received pharmacological pain relief reported more frequently fear of childbirth postpartum. When looking at fear of childbirth postpartum, epidural analgesia with continuous infusion does not seem to be preferred over remifentanil-PCA as method of pain relief.

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ADDITIONAL FILES

Additional file 1. Frequencies of the variables obstetric interventions and complications of women who completed the W-DEQ postpartum

Variable*	**N=315 (%)**
Induction of labour	54 (17)
Augmentation of labour	51 (16)
Assisted vaginal birth	29 (9)
Emergency caesarean section	31 (10)
Post spinal headache	2 (1)
Postpartum haemorrhage	19 (6)
Uterine rupture	0
Eclampsia	0
Amniotic fluid embolism	0
Myocardial infarcation	0
Maternal admission ICU	0
Neonatal admission intensive care	0

*A Woman can have more than one intervention. Rows are not mutually exclusive. ICU: intensive care unit.

Additional file 2. Characteristics of women who completed the W-DEQ antepartum and who did request pharmacological pain relief versus who did not

	Request pain relief N=188	No request pain relief N=186	P value
Gestational age (weeks), median [IQR]	36 [2.4]	36 [2.3]	0.30
Maternal age (years), mean (SD)	32 [4]	32 [4]	0.60
Randomisation allocation RAVEL trial			0.40
Remifentanil-PCA	98 (52)	88 (47)	
Epidural analgesia	90 (53)	98 (53)	
Ethnic origin			0.07
Western	167 (89)	175 (94)	
Non Western	21 (11)	11 (6)	
Education			0.08
≤ Low-medium professional school	44 (23)	31 (17)	
≥ Higher professional school	136 (72)	152 (82)	
Unknown	8 (4)	3 (2)	
Body mass index (kg/m^2) mean (SD)	24 [3.8]	23 [3]	0.10
Parity			<0.001
0	153 (82)	109 (59)	
≥1	35 (19)	77 (41)	
Pain relief received			<0.001
No	33 (18)	186 (100)	
Yes	156 (82)		
Remifentanil-PCA	*80 (43)*		
Epidural analgesia	*72 (36)*		
Other (opioid)	*3 (2)*		
W-DEQ A score (level of fear of childbirth)			0.15
<85 (low-medium fear of childbirth)	168 (89)	174 (94)	
≥85 and <100 (intense fear of childbirth) & ≥100 (very intense/fobic fear of childbirth)	20 (11)	12 (7)	
HADS score antepartum			0.12
< 11	176 (96)	169 (92)	
≥ 11	7 (4)	14 (8)	
missing	5	3	
Previous first trimester loss			0.90
No	139 (74)	139 (75)	
Yes	49 (26)	47 (25)	
Previous assisted vaginal delivery			0.16
No	181 (96)	173 (93)	
Yes	7 (4)	13 (7)	

IQR: interquartile range; SD: standard deviation

Additional file 3. Univariable analyses: association between method of pain relief and fear of childbirth reported postpartum

Variable	Fear level postpartum: no fear of childbirth (<85) N = 278; n (%)	Fear level postpartum: (very) intense fear of childbirth (≥85) N = 37; n (%)	OR (95% CI)	*p*-value
Pain relief				*0.002*
None* [reference]	174 (63%)	14 (38%)		
RPCA or EA	104 (37%)	23 (62%)	2.8 (1.4-5.6)	0.005
RPCA	*63 (23%)*	*9 (24%)*	*1.8 (0.7-4.3)*	*0.20*
Epidural	*41 (15%)*	*14 (38%)*	*4.2 (1.9-9.6)*	*0.001*
Parity				
Nulli [reference]	190 (68%)	32 (87%)		
Multi	88 (32%)	5 (14%)	0.34 (0.1-0.9)	0.03
Maternal age (years)			0.93 (0.9-1.0)	0.09
Education level (professional school)				
≤ medium [reference]	41 (15%)	12 (32%)		
≥higher	229 (82%)	24 (65%)	0.36 (0.2-0.8)	0.009
Missing	8	1		
Duration of labour (active labour-birth)			1.1 (1.0-1.2)	0.007
Median (hours)	270 (97%)	31 (84%)		
Missing	8 (3%)	6 (16%)		
Obstetric intervention/complication**			2.5 (1.2-5.2)	0.01
No [reference]	161 (58%)	13 (35%)		
Yes	117 (42%)	24 (65%)		
Hospital Anxiety Depression Scale antepartum (depression and/or anxiety)				
HADS <11 [reference]	259 (93%)	33 (89%)		
HADS ≥11	10 (4%)	3 (8%)	2.4 (0.6-9.0)	0.21
Missing	9			
Fear level antepartum				
Low-medium (<85) [reference]	255 (92%)	29 (78%)		
High (≥85 and <100) & severe (≥100)	16 (6%)	8 (22%)	4.4 (1.7-11.2)	0.002
Missing	7	0		

CHAPTER 5

Practice variation in the use of remifentanil during labour
An overview of the application in Dutch Hospitals

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ABSTRACT

Objective To survey (a) the frequency of the use of remifentanil patient controlled analgesia (PCA) during labour in the Netherlands; (b) considerations of gynaecologists whether or not to offer remifentanil-PCA; (c) target population for remifentanil-PCA and (d) the application of maternal monitoring.

Design Descriptive survey.

Method A questionnaire was sent to all 81 Dutch hospitals with a labour ward. The following subjects were covered: (a) available methods for pharmacological pain relief; (b) considerations of gynaecologists whether or not to offer remifentanil-PCA; (c) target population for remifentanil-PCA; (d) maternal monitoring and (e) the hospital's birth data for the year 2016. The hospital pharmacist was asked for the number of remifentanil ampuls dispensed in 2016-2017.

Results The questionnaire was completed by 81 gynaecologists (100% response rate). Remifentanil-PCA was available in 59 out of 81 (73%) hospitals with a mean use of 23% of the births (range 16-56%) in those units. In 34 (58%) of these hospitals, remifentanil-PCA was available for all women, and in 25 (42%) it was for a selected group of women. Most frequently mentioned considerations for offering remifentanil-PCA were 'a need for an alternative for epidural analgesia' and 'at the request of pregnant women' reported a respective 55 (93%) and 46 (78%) times. In hospitals where remifentanil-PCA was not offered, the following motives were given for this policy: 'epidural analgesia is the best method of pain relief during labour'; 'risk of serious maternal complication'; and 'insufficient possibilities for observation at the labour ward'.

Conclusion A large variation between Dutch hospitals exists in the application of remifentanil-PCA during labour. In the majority of the hospitals, remifentanil-PCA is available for all women. The most common motives mentioned by gynaecologists for its use are 'a need for an alternative for epidural analgesia' and 'at the request of pregnant women'.

BACKGROUND

Patient controlled analgesia with remifentanil (remifentanil-PCA) is a popular method of pain relief during labour (1–4). Remifentanil is a μ–receptor agonist with a fast onset of action and a short half-life (3-4 minutes)(5). It passes the placenta and is rapidly metabolised and redistributed by the fetus (6). These properties make remifentanil-PCA eligible to use as pharmacological pain relief during labour and is therefore used worldwide, although remifentanil-PCA is used off-label (7). Using remifentanil is associated with a risk of hypoventilation and respiratory depression (5). Epidural analgesia is the most effective method of pain relief during labour, though this invasive method increases the risk of maternal fever, maternal hypotension and assisted vaginal delivery (8–10).

The Guideline for pain relief during labour of the Dutch Society of Obstetrics and Gynaecology (NVOG) and the Dutch Society of Anaesthesiology (NVA) dating from 2008, recommended the use of remifentanil-PCA only in the context of scientific research because of insufficient evidence about its efficacy, side effects and potential risks of serious maternal complications of remifentanil-PCA. Despite this, the Dutch Health Care Inspectorate concluded in 2013 remifentanil-PCA was used at Dutch labour wards with varying conditions for safe use. This led to the introduction of the 'Standard Operating Procedure' (SOP) at labour wards for the use of remifentanil-PCA. The SOP states a free choice between remifentanil-PCA and epidural analgesia is never an option (11).

The use of remifentanil-PCA as a labour analgesic in the Netherlands is not registered and the current practice of remifentanil-PCA is not investigated since the introduction of the SOP and the RAVEL-studies ('RAVEL' stands for 'remifentanil patient controlled analgesia versus epidural analgesia during labour). In these studies, women who received remifentanil-PCA showed to be less satisfied with their experience of labour pain in comparison with women who received epidural analgesia (12,13).

We investigated (a) the frequency of the use of remifentanil-PCA during labour in the Netherlands in 2016 and 2017; (b) considerations of gynaecologists whether or not to offer remifentanil-PCA; (c) target population for remifentanil-PCA and (d) the application of maternal monitoring.

METHODS

An online survey (LimeSurvey) was sent by email to one gynaecologist in all 81 Dutch hospitals with a labour ward. The survey consisted of 15 both free text and multiple-choice questions. The survey enquired details about available methods of pharmacological pain relief; details about who are eligible for remifentanil-PCA during labour; considerations of gynaecologists on whether or not to include remifentanil-PCA in the hospital protocol for pain relief during

labour based on statements with a 5-point Likertscale (1= strongly agree; 5 = strongly disagree); registration of maternal monitoring and Perinatal Registry data from 2016. In the analysis we combined the answer 'strongly agree' with 'agree' and 'strongly disagree' with 'disagree'.

We contacted hospital pharmacists to provide us with the number of ampuls of remifentanil that had been prescribed in 2016 and 2017 to the labour wards. We converted the ampuls to the number of patients that used remifentanil-PCA using the local hospital protocol. When necessary, two reminders were sent with an interval of two weeks after the initial survey was sent. When there was no response after these reminders, the respective gynaecologist and hospital pharmacists were approached by phone. Finally, we informed in every hospital if they could provide us with the local protocol of the preparation of remifentanil-PCA. For analysis we used descriptive statistics; analysis were performed using the program R (version 1.0.136) for Mac OS-X. The Medical Research Ethics Committee (MREC) issued a 'No grounds for non-acceptance' (W17_428#17.496) for this research.

RESULTS

Use of remifentanil-PCA

In the period between January and March 2018 all 81 gynaecologists returned de survey. The response rate of the pharmacists was 83% (49/59). In 59 (73%) of the 81 hospitals, remifentanil-PCA was available at any desired moment according to the protocol pain relief during labour. Of these 59 hospitals, eight hospitals used remifentanil-PCA for more than ten years, 29 hospitals used it between six and ten years, 22 hospitals for a maximum of five years and two hospitals stopped using remifentanil-PCA. Twenty hospitals never used remifentanil-PCA. Five hospitals used a background infusion next to the remifentanil-PCA bolus. Epidural analgesia was available 24/7 in all 81 hospitals, nitrous oxide and pethidine were available in respectively seven (9%) and 76 (94%) of the 81 hospitals.

Data of the Perinatal Registry 2016 as well as data from pharmacists were available for 45 hospitals. In these 45 hospitals, 73,060 (62%) of all secondary care deliveries in 2016 in the Netherlands took place (14). Remifentanil-PCA and epidural analgesia were used respectively 15,459 times (mean 23%, range 16-56), and 20,000 times (mean 27%, range 7-57) and 28,098 women delivered without using pharmacological pain relief (mean 37%, range 25-66)(Figure 1). In 19 of the 22 hospitals where remifentanil-PCA is not used as a labour analgesic, epidural analgesia was used in 7,312 (mean 29%, range 16-42) of the 24,521 deliveries. In 2017 remifentanil-PCA was used 17,430 times in these 45 hospitals. Presumed that the total number of deliveries in 2017 was the same as in 2016, we can conclude that remifentanil-PCA was used in an average of 26% (range 19-51%) of the secondary care deliveries in 2017.

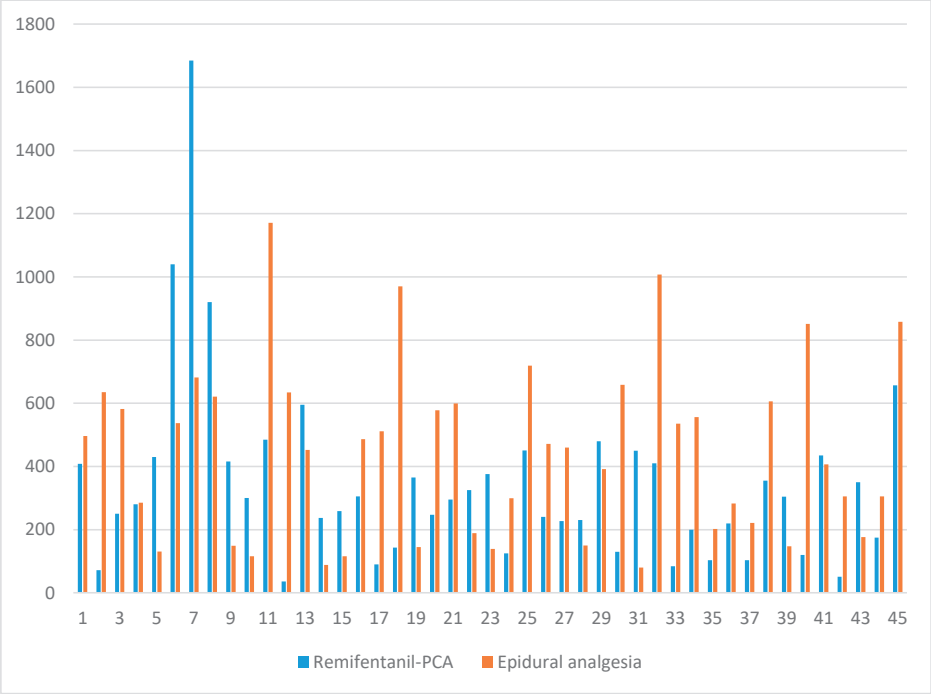

Figure 1. Number of women per hospital who used remifentanil patient controlled analgesia or epidural analgesia in 2016

Considerations gynaecologists

Of the 59 hospitals where remifentanil-PCA was available during labour, it was available for all women in 34 (58%) hospitals and in 25 (42%) for a select group of women only. The most mentioned selection criteria were: nulliparous women with more than six centimetre dilation, multiparous women, women who do not wish to receive epidural analgesia or those with a contra-indication for epidural analgesia. The most mentioned considerations to offer remifentanil-PCA were: 'desirability of an alternative for epidural analgesia' (in 55 (93%) of the 59 hospitals) and 'at the request of pregnant women' (46 hospitals (78%)).

In the 25 hospitals where remifentanil-PCA was available for a select group of women; 'labour to far progressed for epidural analgesia' was most mentioned as a consideration (22 times (88%)). In 14 (56%) of the 25 hospitals where remifentanil-PCA is selectively used, the restrictions of the SOP were not a motive for this choice, nor was the NVOG/NVA guideline for pain relief during labour in 11 (44%) hospitals.

Considerations of gynaecologists not to offer remifentanil-PCA as a method of pain relief during labour were: 'epidural analgesia is the best method of pain relief during labour' (20 of 22 hospitals), 'risk of severe maternal complication' (17 hospitals); 'insufficient possibilities for observation at the labour ward' (14 hospitals); 'sufficient other methods for pain relief during labour' (13 hospitals); 'NVOG/NVA guideline advises not to offer remifentanil-PCA regularly'

(11 hospitals) and 'anaesthetists do not wish to offer remifentanil-PCA as a method of pain relief during labour' (9 hospitals)(table 1).

Table 1. Considerations of gynaecologists whether or not to offer remifentanil-PCA in the protocol pain relief during labour

Hospital policy	Number of hospitals	Considerations gynaecologists (times mentioned)*
All women	34	Desirability of an alternative for epidural analgesia (33)
		At the request of pregnant women (29)
Select group of women	25	Desirability of an alternative for epidural analgesia (22)
		At the request of pregnant women (17)
		Labour to far progressed for epidural analgesia (22)
		Women who do not wish epidural analgesia (18)
Not available	22	Epidural analgesia is the best method of pain relief during labour (20)
		Risk of severe maternal complication (17)
		Insufficient possibilities for observation at the labour ward (14)
		Sufficient other methods for pain relief during labour (13)
		NVOG/NVA guideline advises not to offer remifentanil-PCA regularly (11)
		Anaesthetists do not wish to offer remifentanil-PCA as a method of pain relief during labour (9)

Remifentanil-PCA = remifentanil patient controlled analgesia
NVOG = Dutch Society of Obstetrics and Gynaecology
NVA = Dutch Society of Anaesthesiology
* The numbers are the result of a survey returned by one gynaecologist from each of the 81 Dutch hospitals with a labour ward

Monitoring

The SOP led to a change in dosage and monitoring in 44 (75%) of the 59 hospitals that offer remifentanil-PCA. The oxygen saturation and heart rate were monitored continuously in respectively 51 (86%) and 40 (68%) of these hospitals; the respiratory rate was monitored intermittently in 40 (68%) of the hospitals and in 12 (20%) continuously. The blood pressure was monitored in all 59 hospitals, the level of sedation in 45 (76%) and capnography in four (7%) of the 59 hospitals (table 2).

Table 2. Maternal monitoring in patients receiving remifentanil-PCA during labour
Per parameter is viewed whether or not and how many hospitals register the parameter

Parameter	Mode of registration; n		
	Continuously	**Intermittent**	**None**
Oxygen saturation	51*	8	0
Heart rate	40*	19	0
Respiratory rate	12†	40*	7
Blood pressure	-	59*	0
Level of sedation	-	45*	14
End-Tidal CO_2	3†	1	55

Remifentanil-PCA = remifentanil patient controlled analgesia
* Maternal monitoring according to Standard Operating Procedure (SOP)
† Optional registration as long as no oxygen is administered

DISCUSSION

This is the first study focusing on the current practice of remifentanil-PCA in the Netherlands since the introduction of the SOP and the RAVEL-trials (11–13). Remifentanil-PCA is applied on a large scale, and is available for all women in most of the Dutch hospitals, contrary to what the SOP and NVOG/NVA guideline for pain relief during labour advise. After epidural analgesia it is the most used method for pain relief during labour. In hospitals where remifentanil-PCA is available, the application varies from 16 to 56% of all deliveries. The majority of gynaecologists explained that remifentanil-PCA is available for all women which is in contrast with the target group described in the SOP and in the NVOG/NVA guideline. Also, a considerable number of hospitals use a different dosage and maternal monitoring than the SOP prescribes. Considerations of gynaecologists to offer remifentanil-PCA like 'desirability of an alternative for epidural analgesia' and 'at the request of pregnant women' are consisted to earlier findings in the literature (15,16).

Strengths and limitations

The strength of this study is the 100% response rate, which provides a complete overview of the current use of remifentanil-PCA in the Netherlands. This is the first study since the introduction of the SOP to the variation of the use of remifentanil-PCA and the compliance to the indications according to the SOP and the NVOG/NVA guideline.

A limitation of this study is that not every hospital was able to provide data of the hospital pharmacists. Next to this, we made an estimation of the number of patients who have used remifentanil-PCA based on the number of ampuls prescribed by the hospital pharmacists. It is possible this is an over- or underestimation of the use of remifentanil-PCA. On the one hand because it is possible that two ampuls have been used for one patient or because remifentanil-PCA has been prepared but not used because the patient reached full dilation. On the other hand,

an ampul of two milligrams can be split for use for two patients. Also, when we inquired for maternal monitoring, we did not specify the answer 'intermittent registration' to a frequency.

It is disturbing that, despite the risks of remifentanil-PCA, the application of this method of pain relief and the compliance to the SOP are not systematically evaluated. To consider the adjustment to the SOP and the NVOG/NVA guideline, it is necessary to combine the results of this study with data from earlier research about the effectiveness and the side effects of remifentanil-PCA (4,12,13). For a complete overview, serious adverse events attributed to the use of remifentanil-PCA should also be considered. Our research group is evaluating this at this moment, the results thereof are beyond the scope of this article.

CONCLUSION

There is considerable variation in the use of remifentanil-PCA during labour in the Netherlands, varying from 0 to 56% per hospital. Remifentanil-PCA is available for all women in the largest part of the hospitals. The most important considerations of gynaecologists to offer remifentanil-PCA are 'desirability of an alternative for epidural analgesia' and 'at the request of pregnant women'.

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CHAPTER 6

Serious adverse events attributed to remifentanil patient controlled analgesia during labour in The Netherlands

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ABSTRACT

Background During labour, remifentanil patient-controlled analgesia is used as an alternative to neuraxial analgesia. Remifentanil is associated with hypoventilation and respiratory depression but the frequency of serious maternal and neonatal adverse events is unknown. The aims of this study were to estimate the number of serious adverse events attributed to the use of remifentanil patient-controlled analgesia during labour in The Netherlands and to investigate the circumstances (e.g. monitoring, practice deviations) of these events and the subsequent management.

Methods In a nationwide survey among obstetricians, anaesthetists and clinical midwives the frequency of serious adverse events was assessed. A questionnaire was sent by email to all 61 Dutch hospitals in which remifentanil patient-controlled analgesia is, or has been, available for labour analgesia. All reported cases were assessed independently by two expert teams.

Results We received information from all hospitals. After independent assessments, 17 cases of single maternal desaturation; 10 maternal cases of apnea, bradycardia and/or cardiac arrest; and two neonatal cases of respiratory depression, over a period of more than 10 years of remifentanil patient-controlled analgesia use, were identified as a serious adverse event. All serious adverse events were resolved without irreversible damage.

Conclusion The risk of a potentially life-threatening serious adverse event attributed to remifentanil patient-controlled analgesia seems to be low. All patients recovered without deficit. Adherence to strict monitoring and the attendance of trained healthcare providers is required to safely use remifentanil for labour analgesia.

INTRODUCTION

Epidural analgesia is considered to be the most effective and is a preferred method of labour analgesia (1,2). Remifentanil, a synthetic opioid, has a fast onset of action, short half-life and is metabolised and redistributed quickly by the fetus (3,4). These properties make remifentanil patient-controlled analgesia (PCA) an alternative to epidural analgesia when not available, not desired or contraindicated, although its use is considered off-label (5). Remifentanil PCA has been used for labour analgesia over the past decade in Europe (6–11). However, remifentanil-PCA has been associated with hypoventilation and respiratory depression (3). Several case reports have been published in which maternal respiratory arrest, and/or a cardiac arrest, was attributed to the use of remifentanil PCA (12–17). Moreover, Kan et al. found that remifentanil crosses the placenta rapidly and may theoretically cause neonatal respiratory depression (3). A recent Cochrane review recommended further research on the maternal and neonatal safety of remifentanil PCA during labour (18).

Due to these safety concerns, remifentanil PCA is considered to be a controversial method of labour analgesia (19,20). In the Dutch Societies of Obstetrics and Gynaecology and Anaesthesiology guideline for labour analgesia, the risk of incautious use of remifentanil PCA is mentioned (2,11). Safety concerns and the variety of remifentanil PCA administration protocols for labour analgesia led to mandatory implementation of a multidisciplinary Standard Operating Procedure (SOP) by the Dutch Health Care Inspectorate, in every Dutch hospital. The SOP was composed and introduced by the Dutch Societies of Obstetrics and Gynaecology, Midwifery, Anaesthesiology and Hospital Pharmacists in 2014 (21). Since introduction of this SOP, no evaluation has been performed to assess the use of remifentanil PCA during labour.

The frequency of serious adverse events (SAEs) such as maternal apnoea, bradycardia and cardiac arrest, as well as neonatal respiratory depression, bradycardia and cardiac arrest as a result of remifentanil PCA during labour is unknown. More knowledge about the frequency of maternal and neonatal SAEs attributed to the use of remifentanil PCA during labour and the circumstances of these cases is needed to validate this as a suitable method of labour analgesia and for the counselling of pregnant women.

The aims of this study were to estimate the number of serious maternal and neonatal adverse events attributed to the use of remifentanil PCA during labour; and to investigate the clinical circumstances (e.g. monitoring, deviations from the SOP) of these cases and the procedures followed in managing the events.

METHODS

Design

We conducted a descriptive study. Information about possible SAEs attributed to the use of remifentanil PCA was collected through an online questionnaire. The circumstances of the possible SAEs, and the procedures followed after the events, were assessed independently by two expert teams, each of which consisted of an obstetrician, an anaesthetist and a clinical midwife. Our study did not require formal approval of an ethics committee, according to Dutch law, as confirmed by the ethics committee of the Academic Medical Centre in Amsterdam (ref. nr. W17_427#17.495).

Data collection

We developed the online questionnaire in LimeSurvey (22). Links to the questionnaire were sent by email to healthcare providers involved in the administration of remifentanil PCA, namely one obstetrician, one anaesthetist and one clinical midwife in each of the 61 Dutch hospitals where remifentanil PCA is or has been available for labour analgesia. We have previously reported, from a survey about remifentanil PCA practices sent to obstetricians in all 81 Dutch hospitals with a labour ward, that 59 (73%) have remifentanil PCA available, and that in two hospitals it had previously been available (9). Of these 59 hospitals, six are academic, 26 non-academic teaching and 27 are non-teaching hospitals. One academic hospital used remifentanil PCA only during the RAVEL trials between 2011-2013 and one non-academic teaching hospital discontinued remifentanil PCA in 2012 (9). Before sending the questionnaire we contacted all hospitals to inquire about the most suitable obstetrician, anaesthetist and clinical midwife in each institution to answer the questionnaire. After the first invitation, two reminder emails were sent to each potential respondent, each after two weeks. In case of no response after these reminders, we made a telephone approach.

The questionnaire included two multiple-choice questions with the option of free text. To ensure validity and comprehensiveness, we piloted the questionnaire among four obstetricians, four anaesthetists and four clinical midwives from both academic and non-academic hospitals. This pilot led to some linguistic revisions.

After revisions the questions were: “To the best of your knowledge, have there been any incidents and/or complications at your institution of maternal respiratory depression or respiratory arrest and/or bradycardia or cardiac arrest, possibly as a result of the use of remifentanil PCA during labour (since the start of the use of remifentanil-PCA for labour analgesia in your department)?” and “To the best of your knowledge, have there been any incidents and/or complications at your institution of neonatal respiratory depression or respiratory arrest and/or bradycardia or cardiac arrest, possibly as a result of the use of remifentanil PCA during labour (since the start of the use of remifentanil-PCA for labour analgesia in your department)?” (Additional File 1). We adopted a broad description of an SAE, aiming to substantiate all potential

cases. If the respondent reported a possible SAE, we requested further details about the situation in which the possible SAE had occurred. Furthermore, if a possible SAE was reported, we asked for the name of the healthcare provider responsible for the case.

We contacted the healthcare provider for additional information, preferably based on the patient record, using a checklist. The checklist contained items such as the calendar year of the SAE, the maternal and neonatal vital signs, rescue treatments, medications and obstetric outcomes. We asked for specific details, based on previous case reports, such as use of supplemental oxygen or a background remifentanil infusion, administration of an opioid less than four hours before the start of remifentanil-PCA, one-to-one care and if retrospective checks for pump and medication failure had been conducted (Additional File 2)(12–17). The respondents could select the option that they were unaware of any SAE or that she/he did not have information about possible SAEs. In the latter situation we requested the contact details of a colleague to verify the answer. Furthermore, the respondent had the option to state that she/he did not want to answer the questions. Details of the women with SAEs were reported anonymously, and we based our information only on written and verbal information from the healthcare providers. References to the identity of the caregiver and the hospital were deleted prior to analyses. If we received more responses from the same hospital we contacted the respondents to verify whether these were duplicated reports of the same cases.

Standard Operating Procedure (SOP)

The Dutch SOP prescribes requirements for the use of remifentanil PCA, such as education for healthcare providers, the procedure to obtain informed consent, maternal monitoring requirements, preparation for the application of the method, treatment for complications and documentation (Additional File 3).

Assessment

Since the literature does not provide an operational definition of an SAE related to remifentanil use, we established two expert teams. The first expert team had two tasks. Prior to data collection they were asked to define maternal and neonatal respiratory depression and arrest, bradycardia and cardiac arrest, based on the literature and their clinical experience (23). Maternal respiratory depression or arrest was defined as an oxygen saturation of 85% or less ($SpO_2 \leq 85\%$) and/or an apnoea lasting at least 20 seconds (respiratory rate ≤ 3/minute) and/or the application of bag-mask ventilation. Maternal bradycardia was defined as a heart rate of 50 beats/min or less and cardiac arrest as the absence of maternal pulse, for which cardiopulmonary resuscitation (CPR) was applied; and neonatal respiratory depression or arrest as apnoea for which bag-mask ventilation was applied. The definition of neonatal bradycardia was a heart rate of 60 beats/min or less and cardiac arrest as the absence of neonatal pulse, for which neonatal cardiopulmonary resuscitation was applied.

Subsequently, both expert teams independently reviewed all possible SAEs and using any additional information provided, assessed whether a reported case was likely an SAE attributed to the use of remifentanil PCA. The expert teams used the written information and the information collected via checklists, and the definitions determined by the first expert team for these assessments. Discrepancies were resolved by a third anaesthetist who independently judged these cases. In some cases the additional information was insufficient to determine whether it had been an SAE; for this reason, the responses required interpretation. Additionally a paediatrician was contacted to independently review all neonatal cases. To ascertain complete reporting of these SAEs attributed to remifentanil PCA, we checked two other sources where SAEs could have been registered or reported, these being the Dutch Health Care Inspectorate and Lareb (The Dutch Pharmacovigilance Centre). This information was obtained by personal contact (SL).

RESULTS

Number of serious adverse events (SAEs)

Between January and March 2018 the questionnaire was completed by 61/61 (100%) obstetricians; 54/61 (89%) anaesthetists and by 59/61 (97%) clinical midwives. We received 36 reports of a possible maternal SAE and four reports of a possible neonatal SAE attributed to the use of remifentanil PCA for labour analgesia. Additional information about the reported cases was retrieved from the patient record for 18 maternal and one neonatal case; and was based on the respondent's memory for 12 maternal and three neonatal cases. For six maternal cases the respondents declined consent to be approached for additional information. Information was mostly provided by the healthcare providers responsible for the case of the possible SAE. Both expert teams assessed all maternal and neonatal reports. Figure 1 shows the outcome after the assessments by the expert teams.

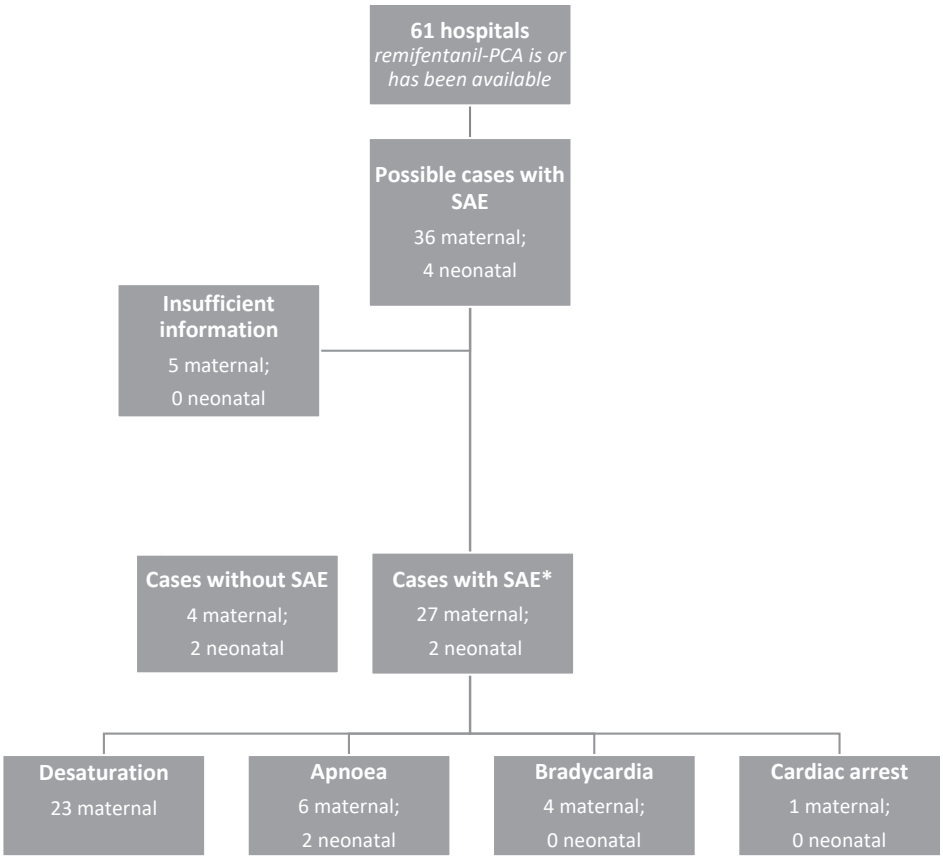

Figure 1. Flowchart of cases with one or more maternal or neonatal serious adverse event(s)
*One case could contain more than one serious adverse event. SAE: serious adverse event; remifentanil-PCA: remifentanil patient controlled analgesia. Desaturation= saturation ≤85%; maternal apnoea= respiratory rate ≤ 3/minute; neonatal apnoea= need for bag-mask ventilation; maternal bradycardia= heart rate ≤ 50 beats/minute; cardiac arrest= absence of maternal pulse.

Of the 23 maternal cases involving oxygen desaturation, 17 were single events and were treated by encouraging breathing and/or discontinuation of remifentanil PCA and/or supplemental oxygen. In five cases desaturation occurred in combination with apnoea and in all these five cases a background infusion was used simultaneously with remifentanil PCA boluses. In two cases of apnoea the administration of remifentanil PCA was discontinued and supplemental oxygen was applied. In one case bag-mask ventilation was applied and naloxone given intravenously. This woman had simultaneous administration of other medications: magnesium sulphate; oxytocin; methyldopa and nifedipine. In one case intubation was performed because effective bag-mask ventilation was not possible and one woman with oxygen desaturation and apnoea was treated with three thoracic compressions, without other interventions. One woman had oxygen desaturation, apnoea and a cardiac arrest, and CPR was applied for three minutes. In this case, in retrospect, 10 mL of the drug appeared to be missing from the syringe.

An overdose of remifentanil might have been caused by a single error of the PCA pump or during the connection of the perfusor line to the patient (Table 1). All women with an SAE recovered completely, without deficit.

In one neonatal case of apnoea a stiff thorax was diagnosed. This was considered to be the cause of the respiratory depression that necessitated intubation. In the second neonatal case, delivery occurred within three minutes of the last bolus of remifentanil PCA. Five inflation breaths and positive end-expiratory pressure were applied, after which the neonate did not need further resuscitation (Table 1). None of the reported neonatal adverse events occurred in a mother with an adverse event. Both neonates with an SAE recovered completely, with no deficit at the end of the treatment.

Table 1. Maternal and neonatal cases with serious adverse events attributed to remifentanil patient controlled analgesia (RPCA) during labour

Case	Type of serious adverse event(s)	Calender year	Procedures followed
Maternal (17)	Desaturation	2007-2015	None or encouraging to breath; and/or stop RPCA; and/or supplemental O_2
Maternal (2)	Desaturation; apnoea	<2014	Stop RPCA; supplemental O_2
Maternal[a]	Desaturation; apnoea	2014	Stop RPCA; supplemental O_2; bag-mask ventilation (3 minutes); 0,4 mg naloxone iv.
Maternal[b]	Desaturation; apnoea	2013	Stop RPCA; supplemental O_2; intubation
Maternal	Desaturation; apnoea	2011	Stop RPCA; supplemental O_2; 3 chest compressions
Maternal[c]	Desaturation; apnoea cardiac arrest	2012	Stop RPCA; supplemental O_2; cardiopulmonary resuscitation (3 minutes)
Maternal (3)	Bradycardia	2017	None
Maternal[d]	Bradycardia	2009	Stop RPCA; supplemental O_2; chest compressions (few minutes)
Neonatal[e]	Respiratory depression	2015	Intubation (few hours)
Neonatal[f]	Respiratory depression	2017	5 inflations breaths; positive end-expiratory pressure

[a] administration of $MgSO_4$; oxytocin; methyldopa; nifedipine simultaneously with Remifentanil-PCA (RPCA) during labour; [b] impossibility to achieve effective bag-mask ventilation; [c] error in PCA pump; [d] according to healthcare provider not attributed to RPCA; [e] stiff thorax diagnosed; [f] birth < 3 minutes after last RPCA bolus.
Desaturation= oxygen saturation ≤85%; apnoea= respiratory rate ≤ 3/minute; bradycardia= heart rate ≤ 50 beats/minute; cardiac arrest= absence of maternal pulse. Neonatal respiratory depression= apnoea for which bag-mask ventilation was applied.

Other sources

No cases of maternal or neonatal SAEs had been reported to the Dutch Health Care Inspectorate. Lareb had registered six cases of 'maternal side effects' of remifentanil PCA during labour between 2004 and 2017. This registration consisted of three cases of skin rash; one case of oxygen desaturation; one case of respiratory depression and one case of cardiac arrest. It is

not known if these were among the cases reported by the healthcare providers, or if they were additional cases. Additional information about these cases was not available.

DISCUSSION

Main findings

We studied the number of SAEs attributed to the use of remifentanil PCA during labour in The Netherlands. In our survey among obstetricians, anaesthetists and clinical midwives we identified 27 maternal and two neonatal SAE cases. The 27 maternal cases comprised 23 desaturation events, six apnoea events, four bradycardia events and one cardiac arrest. The two neonatal cases both concerned respiratory depression. In five cases of maternal apnoea, a background infusion was running in addition to remifentanil PCA boluses. All SAEs were managed without lasting harm during the hospital stay.

Interpretation

Our study provides an opportunity to estimate the frequency of SAEs attributed to remifentanil PCA in The Netherlands. Although our observation of SAE frequency is likely to be an underestimation, the risk of an SAE attributed to remifentanil PCA seems to be low. Aaronson et al. found 14 complications in 340 cases of remifentanil PCA use during one year (17). In comparison, 21 000 women per year received remifentanil PCA in The Netherlands in 2016 and in 2017 (9). The frequency of SAEs in this study corresponds to that reported by Melber et al.(24). Nevertheless, despite the introduction of an SOP in The Netherlands, SAEs associated with the use of remifentanil PCA for labour analgesia still occur.

Serious adverse events are acute and severe and necessitate immediate treatment. Strict monitoring during remifentanil PCA and the attendance of trained healthcare providers is required to identify and manage SAEs (21,23,25). Optimal maternal monitoring regimens during remifentanil for labour analgesia remain to be determined (19,26). Weiniger et al. found that only 15% of apnoea events were detected by the threshold trigger of <92%, using a pulse oximetry device (23). This could explain the underestimation of desaturation events. In The Netherlands it is common clinical practice to detect apnoea by measuring oxygen saturation with pulse oximetry during remifentanil PCA use. Most apnoea events reported by Weiniger et al. during remifentanil PCA use were detected by capnography or by the Integrated Pulmonary Index (a combination score from respiratory and heart rates, oxygen saturation and end-tidal carbon dioxide)(23). Messmer et al. found a 10% incidence of extreme oxygen desaturation (<80%) in women using remifentanil PCA and a 70% incidence of desaturation to less than 90%. In all those cases, the woman recovered spontaneously (27). The 17 cases of a single episode of desaturation below 85% in our study are likely to be an underestimation. It is unknown as to what extent one-to-one care is used throughout remifentanil PCA administration, in The

Netherlands. Although, according to the Dutch SOP, one-to-one care is not mandatory after the first hour of remifentanil administration, it is likely that continuous one-to-one care prevents apnoea. A balance between strict maternal monitoring and feasibility for healthcare providers is needed when remifentanil is used for labour analgesia. If maternal monitoring cannot be fully accomplished, remifentanil PCA should not be administered.

In five cases of apnoea (that occurred prior to the introduction of the SOP) a background infusion of remifentanil was used in addition to a bolus demand dose. A background infusion is disallowed in the SOP, so it is surprising that some Dutch hospitals are still using a background infusion (9). In previously reported cases with an SAE, a background infusion was also used (13,15,17). Some of our reported cases included human or technical errors, such as failure of the alarm within the monitoring system; an incorrectly adjusted infusion pump; and an infusion pump error. These probable causes of an SAE are comparable with the studies of Kinney et al. and Aaronson et al., who reported medication errors (13,17). Despite safeguards such as the national SOP, such a safeguard does not prevent some potentially life-threatening errors that can be detected by alert healthcare providers. Since the introduction of the SOP, one maternal case of oxygen desaturation, one maternal case of apnoea, three maternal cases of bradycardia and two neonatal SAEs were described. The woman with apnoea received magnesium sulphate as well as remifentanil, increasing the risk of respiratory depression. According to the SOP, magnesium sulphate is a relative contraindication for the use of remifentanil PCA. Bradycardia may occur, even when SOP guidelines are followed. In addition, systematic registration of the use of remifentanil PCA, as well as of SAEs, is required in order to be able to evaluate the safety of remifentanil PCA.

Strengths and limitations

This is the first study to have investigated SAEs attributable to remifentanil PCA during labour in The Netherlands. The main strength of the study is the excellent response rate. We received information from all hospitals where remifentanil-PCA was or is used for labour analgesia, and also reports of SAEs from the Dutch Health Care Inspectorate and Lareb. Although screening of patient's medical records would have provided a more complete picture of SAEs, this would have been time-consuming and expensive, given the number of times remifentanil PCA was used. Furthermore, all cases were assessed by two independent expert teams and the neonatal cases by a paediatrician, which contributed to the internal validity of the study.

Our study also has weaknesses, in particular that the number of reported SAEs is likely to be an underestimate. A reason for this could be that maternal monitoring, according to the SOP, is implemented by only 28 (48%) of the 59 Dutch hospitals in which remifentanil PCA is available (9,28). In addition, due to the definition of oxygen desaturation used (an $SpO_2 \leq$ 85%), oxygen saturation values between 85% and 94% were not included as events. Finally, response bias could have occurred, as some respondents may have been unaware of SAEs or reluctant to report them. Most of the reported cases date from several years ago and in several,

information was provided without confirmation using the patient's medical record or was too limited to be assessed.

CONCLUSION

In conclusion, the number of reported potentially life threatening SAEs attributed to remifentanil PCA as labour analgesia was low. The adherence to strict maternal monitoring and the attendance of trained healthcare providers are an essential requirement for the safe use of remifentanil PCA during labour.

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ADDITIONAL FILES

Additional file 1.

Survey for serious adverse events attributed to remifentanil-PCA in The Netherlands

1. **To the best of your knowledge, have there been any incidents and/or complications at your institution of maternal respiratory depression or -arrest and/or bradycardia or cardiac arrest possibly as a result of the use of remifentanil-PCA during labour (since the start of the use of remifentanil-PCA for labour analgesia in your department)?**

- No, we did not have any maternal incident and/or complication possibly related to the use of remifentanil-PCA
- Yes, we have had a maternal incident and/or complication, *please describe the situation of the incident and/or complication as completely as possible*
- I am not aware of any maternal incidents and/or complications possibly related to the use of remifentanil-PCA, but unsure whether I would know all of them in our hospital, *is there a colleague who could answer this question? please provide contact details of this colleague*
- I do not want to answer this question

2. **To the best of your knowledge, have there been any incidents and/or complications at your institution of neonatal respiratory depression or -arrest and/or bradycardia or cardiac arrest possibly as a result of the use of remifentanil-PCA during labour (since the start of the use of remifentanil-PCA for labour analgesia in your department)?**

- No, we did not have any neonatal incident and/or complication possibly related to the use of remifentanil-PCA
- Yes, we have had a neonatal incident and/or complication, *please describe the situation of the incident and/or complication as completely as possible*
- I am not aware of any neonatal incidents and/or complications, but unsure whether I would know all of them in our hospital, *is there a colleague who could answer this question? please provide contact details of this colleague*
- I do not want to answer this question

Additional File 2.

Checklist for additional information

Calendar year of the case
Time between start remifentanil-PCA and SAE? (minutes, hours)
Time between start SAE and signalise of it; how long did it take? (minutes, hours)
How was the SAErecognized? (monitor alarm; nurse, midwife in the room; partner/family)
Type of SAE? severe desaturation (<85%); respiratory rate depression (<8 min); apnoea (<3/min); bradycardia; cardiac arrest; other..
Dosage (bolus 20/30/40 µgram; other)
Supplemental O_2 at moment of the SAE?
Lock out time (minute)
Monitoring? (which monitoring was used in this case): Pulse; oxygen saturation; RR; respiratory rate; sedation score; end-tidal CO_2
Which treatment? Stop remifentanil-PCA; supplemental oxygen; bag-mask ventilation; medication; CPR, other..
Maternal outcome?
Neonatal outcome?
Medication (preparation) error
Pump failure
Standard supplemental oxygen
Background infusion of remifentanil
Use of remifentanil-PCA in second stage
Simultaneously use of Entonox
Use of other opioid < 4 hour before remifentanil-PCA
Continuous one-to-one care
Position of the hand/arm (occlusion intravenous cannula)
Chest wall rigidity
Intrauterine death

SAE = serious adverse event

Additional File 3.

Standard Operating Procedure Remifentanil patient controlled analgesia (PCA). Adapted from the Dutch SOP available at https://www.nvog.nl/sop-remifentanil/.

1. Education

Every healthcare provider involved in the administration of remifentanil-PCA is educated in and has knowledge of: pharmacology of remifentanil in pregnant women; possible complications and side effects; prevention and treatment of side effects and complications; Basic Life Support; use of oxygen during remifentanil; resuscitation; indication and contra-indications; the use of the PCA system; providing of adequate information.

2. Indication

Application of remifentanil (PCA) is only recommended if epidural analgesia is contra-indicated. Every hospital must have a local protocol.

The choice for the application of remifentanil-PCA must comply with the following criteria: the decision to administer remifentanil-PCA is made by a doctor/clinical midwife (after informed consent of the patient) and can never be a free choice of the patient; if there is a contra-indication* for the use of remifentanil-PCA another method of pain relief has to be chosen.

*Contra-indications: use of other opioids less than four hours before the administration of remifentanil-PCA; hypersensitivity for opioids; simultaneously use of Entonox and remifentanil. Relative contra-indications: BMI > 40; $MgSO_4$; prematurity < 34 weeks.

3. Informed consent

The doctor/clinical midwife has to inform the patient about: the off-label use of remifentanil; the possible risks for the patient and the neonate, long term effects are unknown. The informed consent of the patient must be recorded in the patient record by the healthcare provider.

4. Preparation for the administration of remifentanil

Remifentanil has to be kept and prepared according to the guidelines (GMPZ3/VMS High Risk Medication); the concentration attributed to the patient is 20 µg/ml.

5. Administration of remifentanil

Remifentanil is administered by a patient controlled analgesia (PCA) system with the option of bolus administration and lock-out time; only bolus administration without background infusion is allowed; separate infusion with check valve; the bolus is 30 µg (1.5 ml); if pain relief is insufficient the bolus can be increased to 40 µg; the lock-out time is at least 3 minutes; duration of bolus injection is at least 30 seconds; after the start of remifentanil-PCA or if the dose has been changed there should be a doctor/clinical midwife in the room of the patient for at least 30 minutes; after that during the first hour of the administration of remifentanil-PCA there should be a midwife/nurse in the room of the patient. Preferably there is one-to-one support during the use of remifentanil-PCA; the administration is

only allowed by the patient herself; the partner/healthcare providers are not allowed to administer remifentanil; routinely use of oxygen is prohibited.

6. Monitoring

Minimum monitoring exists of: continuous measurement of oxygen saturation by pulse-oximetry; continuous measurement of hart frequency and blood pressure every five minutes. Respiratory rate and sedation level every 10 minutes, after the first hour every 30 minutes. Continuous measurement of respiration or capnography is optional as long there is no administration of oxygen. Monitoring must continuously be visible for the doctor/clinical midwife. If there are alarms immediately action must be possible.

7. Report

It is required to provide documentation of: dose and lock-out time; oxygen saturation, hart frequency, sedation level; documentation in the first hour every 10 minutes, after that every 30 minutes; complications.

8. Complications

The most frequent complications are desaturation; hypopnea and bradycardia.

a. If the oxygen concentration is <94% or respiratory rate is <8/minute the bolus injection has to be decreased to 20 µg (1ml) and oxygen has to be applied. The doctor/clinical midwife has to be warned. As soon as the oxygen concentration is >95% and the respiratory rate is >8/minute the oxygen application has to be stoppedb. If the oxygen concentration is still <94% or the respiratory rate is still <8/minute, the administration of remifentanil-PCA has to be discontinued. The doctor/clinical midwife has to be warned.c. If the saturation concentration or the respiratory rate decreases for the second time, the administration of remifentanil-PCA has to be discontinued. The doctor/clinical midwife has to be warned. d. In case of a maternal bradycardia <50/minute the administration of remifentanil-PCA has to be discontinued, oxygen has to be applied and the doctor has to be warned. If necessary 0.5mg Atropine has to be given intravenous.e. If necessary Basic Life Support has to be started and the resuscitation team called.f. In case of oxygen administration or complication the attendance of a healthcare provider in the room of the patient is required.

9. Points of attention

Check the equipment and materials before every administration of remifentanil-PCA (such as pulse- oximetry, PCA pump, oxygen administration); no simultaneously administration of other opioids or Entonox is allowed. Do not use other opioids within four hours before the administration of remifentanil-PCA.

CHAPTER 7

Identifying women satisfied with remifentanil patient controlled analgesia rather than with epidural analgesia: a secondary analysis of the RAVEL trials

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ABSTRACT

Background The RAVEL studies failed to show that remifentanil patient-controlled analgesia (PCA) is equivalent to epidural analgesia with respect to satisfaction with pain relief during labour. Since remifentanil-PCA is less invasive and more readily available than epidural analgesia, we investigated whether we could identify women with a request for pain relief who would be as satisfied with remifentanil-PCA compared to epidural analgesia.

Methods We used data from two randomised controlled RAVEL studies, in which 1,832 women with a low obstetric risk or an intermediate to high obstetric risk were allocated to remifentanil PCA or epidural analgesia in case of a request for pain relief during labour. We developed a multivariable model using logistic regression analysis to identify labouring women who would be satisfied with remifentanil-PCA and other women who would be satisfied with epidural analgesia. We included the following potential predictor-treatment variables in the analysis: education level, ethnicity, age, BMI, previous vaginal delivery, antepartum fear of childbirth, risk category, gestational age, onset of labour, augmentation with oxytocin and dilatation. The outcome was satisfaction with pain relief during labour expressed as area under the curve.

Results The final multivariable model contained treatment and the following variables: education level, ethnicity, age, BMI, previous vaginal delivery, antepartum fear of childbirth, risk category, gestational age, onset of labour, augmentation with oxytocin and dilatation as well as a treatment - ethnicity interaction and treatment - risk category interaction. The model identified 18.3% of the study group as women who would be satisfied with remifentanil-PCA. Using remifentanil in this group and epidural in all others would lead to a mean area under the curve for satisfaction with pain relief of 51.27 (95% CI 48.41-54.23), compared to 50.86 (95% CI 48.06-53.83) when epidural analgesia would be used for all women.

Conclusion We developed and internally validated a multivariable treatment selection model for satisfaction with pain relief during labour. After external validation this model could be used to guide decisions about remifentanil-PCA for labour analgesia.

INTRODUCTION

Childbirth is a painful experience for the majority of pregnant women (1). Worldwide a variety of pain management strategies is being used to cope with and to relieve labour pain. Pharmacological pain relief reduces the pain experienced during labour (2). Epidural analgesia is the most effective method of pain relief during labour, but it is invasive and associated with an increased risk of assisted delivery, maternal fever, maternal hypotension, and urinary retention (1–3). When epidural analgesia is not available, undesired, or contra-indicated, an alternative analgesia is needed. Furthermore, having a choice in labour analgesia is an important element of childbirth satisfaction for women (4–6).

Remifentanil -a synthetic opioid- has a fast onset of action, a short half-life, and is metabolised and redistributed quickly by the fetus (7,8). Intravenous remifentanil patient-controlled analgesia (PCA) thus offers an alternative for labour analgesia but it is associated with desaturation and respiratory depression.

Our group recently reported two randomised controlled trials, one among 1,414 intermediate to high obstetric risk women and one among 418 low obstetric risk women. Both trials compared two pharmacological pain relief methods in case of a request for pain relief during labour: remifentanil-PCA versus epidural analgesia. In these trials satisfaction with pain relief and pain scores were compared over the total duration of labour between women allocated to remifentanil-PCA and those allocated to epidural analgesia. Maternal satisfaction with labour pain scores and pain intensity scores were assessed hourly from the start of active labour until the second stage of labour in all participating women.

Overall, women receiving remifentanil-PCA were less satisfied with their pain relief than women using epidural analgesia (9,10). The question is whether this finding is applicable to all women who request pain relief during labour. Previous research has shown that satisfaction with labour pain and pain relief is a complex process. Patient characteristics such as parity, antepartum fear of childbirth, dilatation, onset of labour, education level and ethnicity could influence satisfaction with pain relief (2,11).

We performed a secondary analysis of the RAVEL trials' data to identify women satisfied with remifentanil-PCA for labour analgesia. We aimed to investigate which baseline characteristics could guide the decision to use remifentanil or epidural analgesia for labour analgesia.

METHODS

Summary of RAVEL studies

We used data collected in the RAVEL studies, two multicentre randomised controlled trials (NTR 2551; NTR 3687)(9,10). Women were randomly allocated to a strategy with remifentanil-PCA or epidural analgesia, in case of a request for pain relief during labour, in a 1:1 ratio. The first

RAVEL study recruited 1,414 pregnant women with an intermediate to high obstetric risk in obstetric-led care (9). The second RAVEL study recruited 418 women with a low obstetric risk, in midwife-led care (10). Women were eligible for the study if they were healthy (low obstetric risk RAVEL study) or if they had a mild systemic disease according the American Society of Anesthesiologists (ASA) physical classification 1 or 2 (intermediate to high obstetric risk RAVEL study) and if they were scheduled for a vaginal delivery after 32 weeks. Women younger than 18 years, women with a contra-indication for epidural analgesia or a hypersensitivity to opioids, and women in whom labour had already started were not eligible. Randomisation took place during pregnancy, before the start of labour.

The protocols of both trials were approved by the Ethics committee of the University Medical Centre Leiden and the boards of the participating hospitals (ref. no. P10.240; 26 July 2012). All participants in the RAVEL trials provided written informed consent.

Treatment

Women allocated to remifentanil-PCA received intravenous remifentanil 30 microgram boluses (solution 20 microgram/ml) with a lockout time of three minutes and without background infusion. Remifentanil-PCA was administered by the parturient herself after an instruction on how to use remifentanil-PCA. It was possible to increase the bolus dosage to 40 microgram in case of insufficient pain relief, or to decrease the dose to 20 microgram in case of excessive side effects. Women allocated to epidural analgesia received epidural analgesia according to the local protocol. If analgesia with the allocated pain method was insufficient according to the woman, a switch to the other pain relief method was allowed.

Outcome

The primary outcome was the area under curve (AUC) for satisfaction with pain relief. Satisfaction with pain relief was measured hourly using a visual analogue scale ranging from 0 to 10 cm (highly dissatisfied or satisfied regarding pain relief, respectively). Higher values indicate more satisfaction.

STATISTICAL ANALYSIS

Model building

We performed an intention-to-treat analysis at the randomisation time as well as at the time of actual request for pain relief. Based on a literature review and expert knowledge we identified the following potential treatment selection markers: women with a low versus intermediate/high obstetric risk (risk category); maternal age at randomisation; ethnicity (white/non-white); body mass index (BMI); women with previous vaginal delivery (no/yes); antepartum fear of childbirth measured by W-DEQ (12). At pain relief request we added several potential treat-

ment selection markers: onset of labour (spontaneous/induction); augmentation with oxytocin (yes/no); dilatation at request for pain relief (cm); gestational age (weeks).

In the RAVEL studies we had missing values for the AUC for satisfaction: 329/890 (37%) in the remifentanil and 446/877 (51%) in the epidural analgesia group (9,10). To increase the statistical power and reduce bias from a complete cases analysis, we used Multivariate Imputations by Chained Equations (MICE) for missing values (13). Twenty datasets were created, we selected the dataset that best resembled the average primary outcome of all sets. We imputed missing data within each trial before merging the datasets, as imputation over trials is not recommended, because association of covariates might differ across the included studies (14). We used the imputed datasets from the two trials and after harmonisation of the variables (markers and outcomes) we merged these datasets.

To investigate potential marker-treatment associations on the outcome AUC for satisfaction with pain relief, we performed univariable analysis and built a series of separate linear regression models containing each individual marker, treatment (remifentanil-PCA versus epidural analgesia during labour) and a marker-by-treatment interaction. To investigate the possibility of non-linear associations for continuous markers, we repeated model building using natural splines up to four degrees of freedom and tested if using splines would improve model fit in terms of Akaike Information Criterion (AIC). We selected markers that showed main effect P-values below 0.10 or marker-by-treatment interaction effect P-value below 0.20 for multivariable model building (15,16). We proceeded to build a multivariable linear regression model by introducing the markers and marker-by-treatment interactions that were significant in the model. We then applied a stepwise backward selection procedure using AIC to construct a parsimonious final model. We internally validated the model by bootstrap resampling (n=1,000). The coefficients were shrunken with an average shrinkage factor, retrieved from the bootstrap.

Model performance

The final model was applied to each trial participant two times, regardless of the treatment they were allocated to in the original trials; once with treatment fixed as remifentanil-PCA and once with treatment fixed as epidural analgesia. This approach results in two counterfactual pain satisfaction scores for each participant. The difference between the two generated scores is the estimated absolute satisfaction difference (17). It indicates how much an individual patient would be satisfied with selecting remifentanil-PCA over epidural analgesia (negative scores) or from selecting epidural analgesia over remifentanil-PCA (positive scores).

To evaluate the performance of the developed treatment selection model we assessed calibration of the calculated satisfaction difference by plotting the average calculated satisfaction difference against the average observed outcome differences in groups defined by the quantiles of the satisfaction difference distribution. Ideally, if the observed effects and predicted effects agree over the whole range of probability differences, the plot will show a diagonal line.

In accordance with the RAVEL trials we assumed that a 10% difference in satisfaction would be clinically relevant given the advantages of remifentanil-PCA described in the introduction

(9,10). Based on this assumption we classified women into those who would be satisfied with epidural analgesia (a positive satisfaction difference of 10% or more with epidural analgesia) and those who would be satisfied with remifentanil-PCA (those who have less than 10% increase in satisfaction with epidural analgesia). We then calculated the average satisfaction difference in the group predicted to be satisfied with epidural analgesia, and the average satisfaction difference in the group predicted to be satisfied with remifentanil-PCA.

We then estimated the average satisfaction in the RAVEL study group while using the model to guide the choice of pain relief. In that case, a woman with less than 10% predicted satisfaction with epidural would receive remifentanil and other women epidural (18). We compared this estimate to the average satisfaction when an epidural analgesia would be used in all women, and to the average satisfaction when remifentanil-PCA would be used in all women. The difference between satisfaction based on our model and these two estimates can be interpreted as the population benefit of using the model to guide the choice of analgesia, in terms of the expected increase in satisfaction with pain relief. We used bootstrapping technique for resampling with replacement (n=1,000) to estimate 95% confidence intervals of the average satisfaction scores. We estimated the size of the subgroup of pregnant women who would be satisfied with remifentanil-PCA.

We performed all steps at two moments separately, at randomisation and at the time of actual request for pain relief. R for Windows (Version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses.

RESULTS

In this study, data of 1,767 of the 1,832 women included in the RAVEL trials were analysed. Of these, 552 of the 890 women in the remifentanil-PCA group and 448 of the 877 women in the epidural analgesia group received pharmacological pain relief. Sixty women had an elective caesarean section; three women were lost to follow-up and two women withdrew informed consent after randomisation, these women were excluded from the analysis (Appendix 1). The flowcharts of the original first and second RAVEL trials are provided elsewhere (9,10). In our analysis, the baseline and labour characteristics of the women were comparable between the remifentanil-PCA and epidural analgesia group, both at randomisation and at request for pain relief (Table 1 & 2).

We first performed the intention to treat analysis at randomisation (n=1,767)(Table 1). This analysis did not result in a reliable and valid model to predict satisfaction with pain relief. We then performed the analysis at the time of request for pain relief during labour (n=1,000)(Table 2).

Table 1. Baseline characteristics at randomisation of participants of the RAVEL studies

	Remifentanil-PCA, *n=890*	**Epidural analgesia, *n=877***
Obstetric risk (%)		
Low	203 (23)	206 (23)
Medium-high	687 (77)	671 (77)
Request pain relief during labour (%)		
No	338 (38)	429 (49)
Yes	552 (62)	448 (51)
Maternal age (years), mean (SD)	31.6 (4.9)	31.7 (4.7)
Ethnic origin (%)		
White	790 (89)	788 (90)
Non-white	100 (11)	89 (10)
Education (%)		
Lower (< high school)	361 (41)	346 (40)
Higher (≥ high school)	529 (59)	531 (60)
Body mass index (kg/m^2), mean (SD)	24 (4.4)	24 (4.5)
Previous vaginal delivery (%)		
No	471 (53)	469 (53)
Yes	419 (47)	408 (47)
Antepartum fear of childbirth, median (IQR)	70 (54-81)	70 (53-82)

PCA: patient controlled analgesia; SD: standard deviation; IQR:interquartile range

The relationship between the markers and satisfaction with pain relief

Tables 3 and 4 present the association between the markers and satisfaction with pain relief. We first looked at the marker by treatment interaction. Among the investigated eleven markers, two markers showed significant interaction with treatment: ethnic origin ($p_{interaction}$=0.004) and obstetric risk ($p_{interaction}$ =0.03). We observed that women of non-white origin compared to white women were less satisfied with remifentanil-PCA (10.5 units less), while if they received epidural analgesia they were more satisfied than white women who got epidural analgesia (6.5 units more)[For remifentanil-PCA the median of the AUC was 22, IQR 10-39; for epidural analgesia the median of the AUC was 23, IQR 8-42]. Similarly, women with intermediate to high obstetric risk were less satisfied with remifentanil-PCA (3.8 units less) and were more satisfied (6.3 units more) if received epidural analgesia. These two variables were selected for further multivariable model building (Table 3).

We then searched for markers which are associated with outcome irrespective of treatment. We could identify seven markers which fulfilled the criteria including education level, previous vaginal delivery, antepartum fear of childbirth score, BMI, gestational age, augmentation with oxytocin and dilatation. These variables were also selected to be included in the multivariable model building (Table 4).

Table 2. Baseline and labour characteristics at request pain relief during labour of participants of the RAVEL studies

	Remifentanil-PCA, *n=552*	**Epidural analgesia, *n=448***
Obstetric risk (%)		
Low	105 (19)	101 (23)
Medium-high	447 (81)	347 (78)
Maternal age (years), mean (SD)	31.5 (5.0)	31.7 (5.0)
Ethnic origin (%)		
White	474 (86)	401 (90)
Non-white	78 (14)	47 (10)
Education (%)		
Lower (< high school)	238 (43)	176 (39)
Higher (≥ high school)	314 (57)	272 (61)
Body mass index (kg/m^2), mean (SD)	25 (4.4)	25 (4.7)
Previous vaginal delivery (%)		
No	250 (45)	191 (43)
Yes	302 (55)	257 (57)
Antepartum fear of childbirth, median (IQR)	69 (54-81)	70 (55-83)
Gestational age at delivery (weeks), median (IQR)	40.1 (38.9-41)	39.9 (38.6-41)
Onset of labour (%)		
Spontaneous	226 (41)	198 (44)
Induction	326 (59)	250 (56)
Augmentation with oxytocin (%)		
No	215 (39)	166 (37)
Yes	335 (61)	282 (63)
Dilatation at request pain relief (cm), median (IQR)	4 (3-5)	4 (3-5)

PCA: patient controlled analgesia; SD: standard deviation; IQR; interquartile range; cm: centimetre

Table 3. Two baseline biomarkers which showed a significant marker by treatment interaction and their associations with satisfaction with pain relief during labour in each treatment options

	Remifentanil-PCA *n=552*	**Epidural analgesia *n=448***	
Biomarkers	**Beta ± Std. Error**	**Beta ± Std. Error**	**P-value marker by treatment interaction**
Ethnic origin *Non-white vs white*	-10.51 ± 3.56	6.54 ± 4.75	0.004
Obstetric risk *Intermediate-high vs low*	-3.76 ± 3.18	6.27 ± 3.48	0.03

Table 4. Association of the baseline biomarkers with satisfaction with pain relief from epidural analgesia versus remifentanil-PCA

Biomarkers	P-value *marker x treatment interaction*	Beta ± SE	P-value *main effect*
Ethnic origin (non-white vs white)	0.004*	-4.75 ± 2.91	0.10
Obstetric risk (intermediate-high vs low)	0.03*	0.50 ± 2.38	0.83
Previous vaginal delivery (yes vs no)	0.61	15.2 ± 1.88	<0.001*
Augmentation with oxytocin (no vs yes)	0.50	-13.8 ± 1.93	<0.001*
Dilatation at request pain relief (cm)	0.92	-3.70 ± 0.57	<0.001*
Gestational age at delivery (weeks)	0.75	2.05 ± 0.64	0.001*
Education (high vs low)	0.47	4.62 ± 1.95	0.02*
Antepartum fear of childbirth score	0.30	-0.10 ± 0.05	0.04*
Body mass index (kg/m2)	0.30	0.39 ± 0.21	0.06*
Maternal age (years)	0.88	-0.25 ± 0.19	0.20
Onset of labour (induction vs spontaneous)	0.87	0.55 ± 1.95	0.78

*Markers with main effect P-values ≤0.10 or marker-by-treatment interaction effect P-value ≤0.20: selected for multivariable analysis.

Development of the multivariable model

Based on the univariable analyses we selected the following variables: education level; previous vaginal delivery; antepartum fear of childbirth score, BMI, gestational age, ethnicity, dilatation, augmentation with oxytocin and risk category, as well as treatment and marker-by-treatment interaction terms for ethnicity and risk category. The final model after stepwise backward selection using AIC criterion with corrected beta coefficients to overcome overfitting is presented in Table 5. The shrinkage factor was 0.945.

Table 5. Multivariable model for the prediction of satisfaction with pain relief at request for pain relief

	Beta*	Std. Error	p-value
Intercept	-16.72	25.42	0.51
Main terms			
Treatment (epidural vs remifentanil)	2.70	3.88	0.47
Risk category (high vs low)	-18.95	3.51	<0.001
Ethnicity (non-white vs white)	-5.68	3.40	0.08
Education level (high vs low)	3.41	1.83	0.05
Previous vaginal delivery (yes vs no)	17.37	2.19	<0.001
Antepartum fear of childbirth score	-0.08	0.05	0.08
BMI (kg/m^2)	0.29	0.20	0.12
Augmentation with oxytocin (no vs yes)	-9.24	1.90	<0.001
Gestational age (weeks)	1.85	0.60	0.001
Dilatation (centimetre)	-3.01	0.54	<0.001
Interaction terms			
Risk category × treatment	5.91	4.31	0.15
Ethnicity × treatment	11.78	5.42	0.02

*Shrunken with an average shrinkage factor of 0.945; Std. error: standard error.

Model performance for identification of women who would be satisfied with remifentanil-PCA

Figure 2 depicts the distribution of the calculated differences in satisfaction with pain relief when using epidural analgesia or remifentanil-PCA. Since the numbers of women in two groups with satisfaction difference of 15 and 21 were low, we combined them in a single group with satisfaction differences equal or above 15.

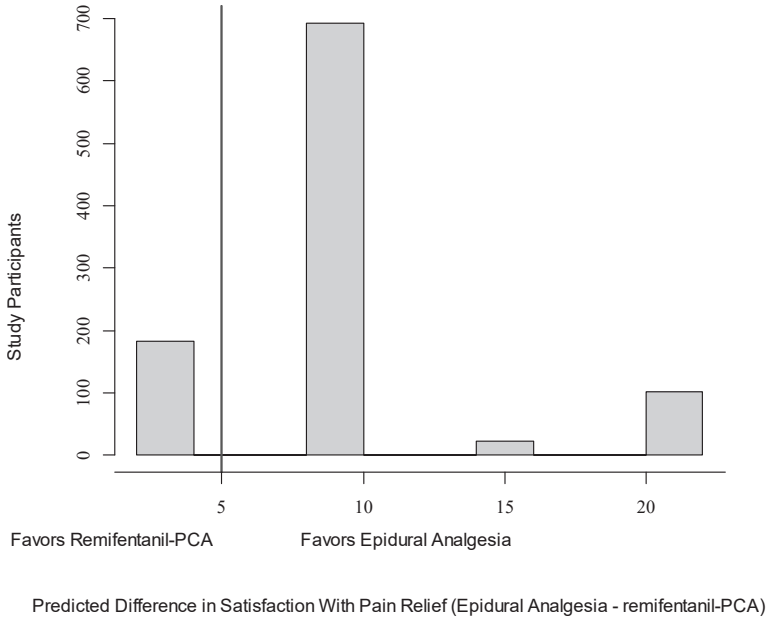

Figure 2. Distribution of the estimated differences in satisfaction with pain relief
X-axis: Satisfaction difference = satisfaction with epidural analgesia minus satisfaction with remifentanil-PCA;
Y-axis: Frequency of study participants

1. Proportion marker positives

Overall, 183 (18.3%) women had a satisfaction difference of less than five and were considered to be satisfied with remifentanil-PCA. The calibration plot, comparing the optimism-corrected expected satisfaction with the observed satisfaction, indicated acceptable calibration (Figure 3).

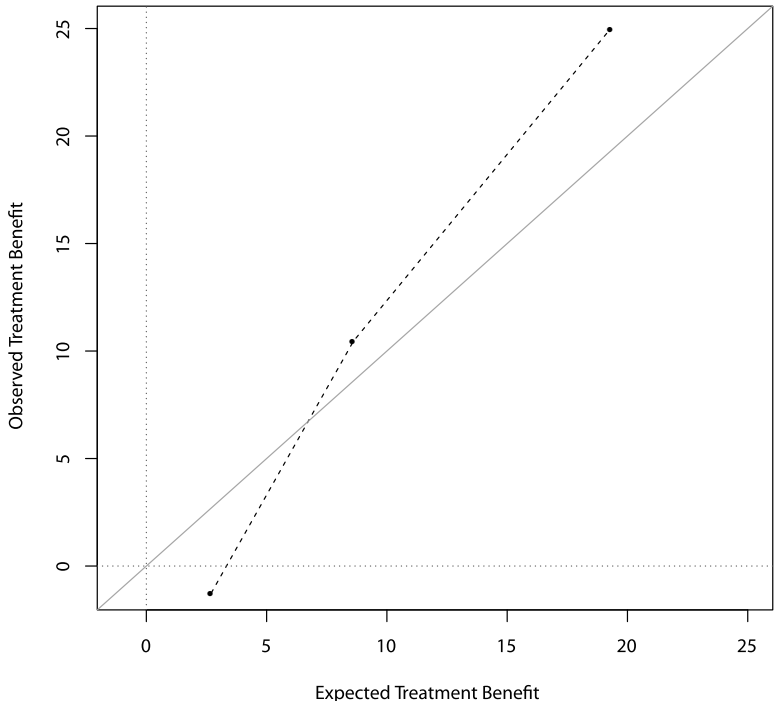

Figure 3. Calibration plot of the multivariable treatment satisfaction difference

2. Average satisfaction of pain management with remifentanil-PCA among marker positives, and epidural analgesia among marker negatives

In women for whom this multivariable model predicts to be satisfied with remifentanil-PCA (marker positive group), the mean estimated satisfaction difference was 2.7 and the observed mean difference in satisfaction was minus 1.25 (in favour of remifentanil-PCA). In women who would be satisfied with epidural analgesia (marker negative group) the mean estimated satisfaction difference was 10.2 and the observed mean difference in satisfaction was 12.73 (in favour of epidural analgesia).

3. Change in population satisfaction score under marker-based treatment strategy

We compared the model-based strategy with the other two strategies, in which either (1) epidural analgesia would be used for all women who request pain relief or (2) remifentanil-PCA would be used for all women who request pain relief.

In a population of women who have a distribution of markers and a response to pain relief similar to women in these trials, we estimated that by applying the proposed model-based pain relief selection, the satisfaction score would be 51.27 (95% CI 48.41-54.23), which is comparable to the satisfaction score if all were treated with epidural analgesia (50.86; 95% CI 48.06-53.83) and higher than if all were treated with remifentanil-PCA (40.70; 95% CI 38.28-43.16). Although

the model-based strategy would lead to a comparable satisfaction score, it could spare 18.3% of women from undergoing the more invasive epidural analgesia.

DISCUSSION

We have developed a multivariable treatment selection model to identify women who would be satisfied with remifentanil-PCA over epidural analgesia for labour analgesia. The model we developed relies on education level, previous vaginal delivery, antepartum fear of childbirth score, BMI, augmentation with oxytocin, gestational age, dilatation at request for pain relief, ethnicity, and risk category. Our model identified 18.3% of the study group as women who would be satisfied with remifentanil-PCA.

Strengths and limitations

A strength of our study is that all included variables are easy to measure and – except for antepartum fear of childbirth - routinely known when the decision which method of pain relief is to be made. Antepartum fear of childbirth could be measured during pregnancy for applying this model. Other strengths are that we used data of randomised trials which were at baseline comparable, the large study groups, and the availability of many variables. We used pre-defined predictors. As such, our approach differs from conventional subgroup analysis in clinical trials (19).

This study also has limitations. We have not yet performed an external validation, for which data of a new trial would be needed. Such a trial should include satisfaction with pain relief measures of women randomly allocated to remifentanil-PCA and to epidural analgesia. We did not yet identify an ongoing randomised controlled trial in the trial registries comparing these two methods with satisfaction with pain relief as outcome measure (20). Another limitation is the relatively long period between randomisation and the treatment in the RAVEL studies. Women were randomised during their pregnancy from 32 weeks gestation onwards in case they would request pain relief during labour. There could have been influence from this strategy at the outcome satisfaction with pain relief.

Interpretation

To our knowledge there is no previous research on this topic of personalized medicine for pain relief during labour. Our study shows that variables influencing satisfaction with pain relief can be identified. Strong predictors were risk category, women with a low obstetric risk were more satisfied with pain relief than women with an intermediate to high obstetric risk; women with a previous vaginal birth were more satisfied with pain relief than women without previous vaginal birth; women with less dilatation at request pain relief were more satisfied with pain

relief than women with more dilatation and women using oxytocin were more satisfied with pain relief than women without oxytocin.

So far, the choice between remifentanil-PCA and epidural analgesia is mainly guided by an assessment from the health care provider – based on clinical experience – and the preference of the woman. In the RAVEL studies the cross-over rate from remifentanil-PCA to epidural analgesia – due to insufficient pain relief – was 13% (9,10). This percentage is comparable with previous research and clinical experience and it shows that it is common to have cross overs when remifentanil-PCA is used for labour analgesia.

Further research on this model is recommended. The first step would be to repeat the analysis with the AUC for satisfaction with pain relief after the start of pain relief instead of using the AUC during the whole period of active labour. Secondly, we could repeat the analysis with fewer variables, provided this would only lead to a marginal decrease in performance, to build a model that is easier to use in clinical practice. The third step would be external validation of the model. Finally, the model should be translated in an accessible instrument, for example an app, to make it accessible for both health care providers and women at the request of pain relief of a woman.

CONCLUSION

After external validation, the multivariable treatment selection model presented here could be helpful to find a balance between administering remifentanil-PCA in the most beneficial way in the light of satisfaction with pain relief and to avoid the more invasive epidural analgesia.

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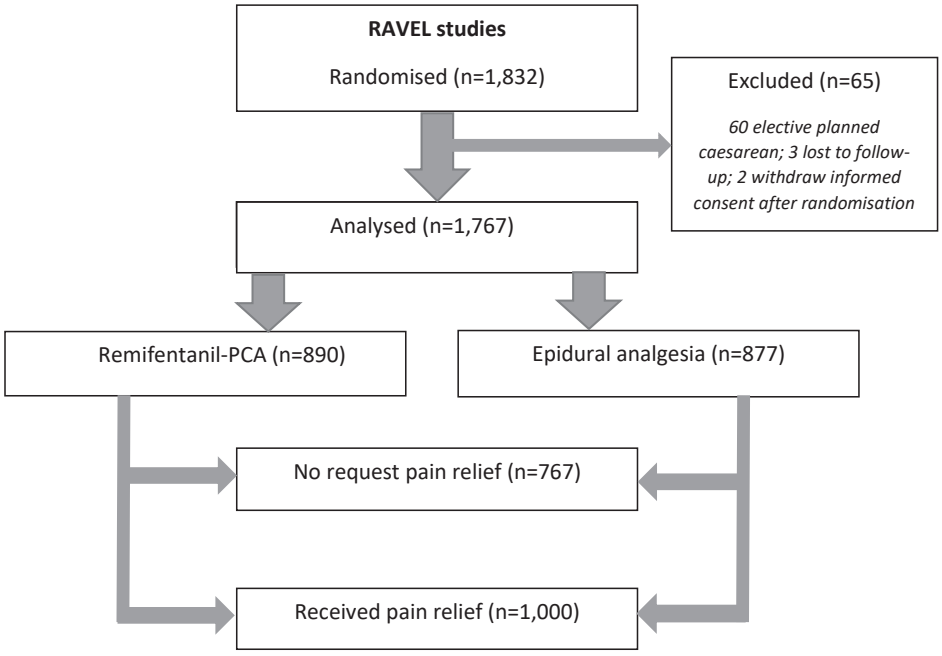

Appendix 1. Flowchart RAVEL studies

CHAPTER 8

Pregnant women's concerns when invited to a randomised trial

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ABSTRACT

Introduction Pregnant women were excluded from clinical trials until the 1990s, but the Food and Drug Administration nowadays allows - and even encourages - responsible inclusion of pregnant women in trials with adequate safety monitoring. Still, randomised trials in pregnant women face specific enrolment challenges. Previous studies have focused on barriers to trial participation in studies that had failed to recruit sufficient participants. Our aim was to identify barriers and motivators for participation in a range of clinical trials being conducted in the Netherlands, regardless of recruitment performance.

Methods We performed a qualitative case control study in women who had been asked in 2010 to participate in one of eight clinical trials during pregnancy or shortly after giving birth. Both participants and non-participants of these clinical trials were invited for a face-to-face interview that addressed motives for participation and non-participation. We started the interview in an open fashion, asking the women for their main motive for participation or non-participation. When no new information emerged in this open part, we continued with a semi-structured interview, guided by a topic list. Transcripts of the interviews were analysed using a constant-comparative approach. Two researchers identified barriers and facilitators for participation, conjoined into main themes.

Results Of 28 women invited for the interview, 21 agreed to be interviewed (12 participants and 9 non-participants). For 5 of 12 participants, contribution to scientific research was their main motive, while 5 had participated because the intervention seemed favourable and was not available outside the trial. Key motives for non-participation (n=9) were a negative association or a dislike of the intervention, either because it might do harm (n=6) or for practical reasons (n=3). Combining the open and topic-list guided interviews we constructed seven main themes that influence the pregnant women's decision to participate: external influence, research and healthcare, perception own situation, study design, intervention, information and counselling, and uncertainty.

Conclusion Among seven main themes that influence pregnant women's decision to participate, uncertainty about scientific research or the intervention was reported to be of considerable importance. Measures should be taken to habituate pregnant women more to scientific research, and further evaluation of opt-out consent deserves attention.

INTRODUCTION

Until the 1990s, pregnant women were often excluded from clinical trials for their own protection (1). However, in general pregnancy does not prevent a woman from acquiring a disease or cure a woman from a disease. Pregnant women may even be more severely affected, for example by infectious diseases (2). Paradoxically, the efforts to protect the fetus from research-related risks by excluding pregnant women from research places both at risk from unstudied interventions (3,4). In the United States approximately 2 in 3 pregnant women are given prescription medication during pregnancy (2). These prescriptions are often based on limited evidence on safety or effectiveness, as results of studies in non-pregnant women may not always apply to pregnant women. The Food and Drug Administration nowadays allows – and even encourages – responsible inclusion of pregnant women in drug trials with adequate safety monitoring (5).

Randomised trials in pregnant women still face specific enrolment challenges. Such studies are unique, since two patients are involved: the mother and her unborn foetus. A woman may refuse treatment for herself if she feels this could harm her baby, or she may feel bound to accept interventions that might benefit the fetus. Additionally, the father's feelings may also influence decision-making about trial participation (6).

Tooher and colleagues have presented a narrative review on factors influencing recruitment for maternal and perinatal trials in which they identified four participant factors that influence recruitment: understanding risk, recruitment process and procedures, participants' understanding of the research process and methodological issues, and patient characteristics (7). Their conclusions were based on a limited number of studies on maternal and perinatal trials, often selected because recruitment was problematic. It is therefore uncertain to what extent these results also apply to other studies. We performed a qualitative study to identify the main barriers and motivators for enrolment in obstetrical trials in the Netherlands, regardless of recruitment performance.

METHODS

Design

We performed a qualitative case-control study. Women invited to one of eight clinical trials during or shortly after pregnancy were invited for a face-to-face interview about their main motives in accepting or declining the invitation to participate. This study is part of the IMPACT project, in which enrolment of patients in trials is studied at different levels (8). Our study did not require formal approval of an ethics committee, according to Dutch law, as confirmed by the ethics committee of the Academic Medical Centre and the Onze Lieve Vrouwe Gasthuis in

Amsterdam. Written informed consent was obtained for all face to face interviews, and verbal consent was obtained for telephone interviews.

Selection of trials and invitation of interviewees

We invited 28 women who had been invited for a clinical trial in obstetrics up to three months prior to the interview. We selected in a 1:1 ratio women who had accepted and women who had declined enrolment. Women were selected from eight multicenter studies running in the Consortium for Women's health and Reproductivity studies that recruited patients between February and June 2010: Allo (9), Apostel I (10), Apostel II (11), Chips (12), WOMB (13), Ppromexil(14), Hypitat II (15), and ProTwin trial (16)(Table 1).

We started by inviting the women most recently invited for a trial, and thereafter selected women less recently invited consecutively (up to 3 months prior to the interview). Women were only eligible if they were still pregnant or their baby was born alive and they could speak Dutch well enough to participate in the interview without an interpreter. We first sent an invitation letter on behalf of the treating gynaecologist and the interviewer introducing the study and the purpose of the interview. The letter indicated that participation or non-participation in the interview was completely voluntary and would not influence their relationship with the treating physician or her treatment in any way. We announced to the women that we would try to contact them by phone about a week after having received the letter, to give additional explanation and answer any remaining questions. At least four attempts to reach the women by phone were made. If she indicated she was not interested and did not want additional information her wishes were respected, and reminders were not sent.

The interview

The interview was conducted face-to-face, unless the respondent explicitly requested a telephone interview, or when the travel time to visit the patient was two hours or more. The interview took place at the patient's home, or in the hospital, whichever was preferred by the interviewee. An interview in the hospital was proposed as the hospital could be perceived as a location were women feel comfortable talking about trial participation, as they might feel uncomfortable inviting the interviewer to their homes, but it could also be because women or their newborns were still admitted.

We started the interview in an open fashion, by asking the women for their main reason for participating or not participating in the trial. Once no new information emerged from the open questioning, we continued with a semi-structured interview guided by a topic list, to cover all aspects that might have contributed to the decision making process. The topic list was developed based on a literature review and with input from experienced gynaecologists and midwives (Appendix 1, Dutch). It included factors related to personal benefit, altruism, knowledge and information about the trial and the trial process, distrust, attitude, organisational

aspects and influence of the social environment. If new topics emerged during the interview, they were added to the topic list (17,18).

Table 1. Overview of trials from which patients were selected for an interview

Trial acronym*	Research question	Treatment arms	Eligible women
Allo[9]	Does antenatal allopurinol administration reduce hypoxic-ischaemic encephalopathy in neonates exposed to intra-uterine asphyxia?	Allopurinol or placebo, antenatal administered to the mother	Women at term in whom the foetus is suspected of intra-uterine asphyxia
Apostel I[10]	Is testing for fibronectin a cost-effective strategy that prevents unnecessary treatment in women with threatened preterm labour?	Tocolytics (nifedipine) or placebo	Patients with symptoms of preterm labour, and a negative fibronectin test and a cervical length between 10-30 mm
Apostel II[11]	Does sustained tocolysis in women with threatened preterm labour reduce neonatal morbidity?	Nifedipine or placebo for 12 days	Women between 24 to 31^{+6} weeks pregnant who have been treated with tocolysis and steroids for preterm birth for 48 hours
CHIPS[12]	Is there a difference on pregnancy loss or NICU admission between less tight and tight control of blood pressure in women with non-severe non-proteinuric pre-existenting hypertension or gestational hypertension remote from term?	'less tight' dBP controlor 'tight' dBP control	Women with non-severe non-proteinuric pre-existing hypertension or gestational hypertension remote from term
Hypitat II[15]	What is the effectiveness and efficiency of induction of labour in women with pregnancy induced hypertension or mild preeclampsia with a gestational age of 34-37 weeks of pregnancy, as compared to expectant management under regular monitoring?	Induction of labor or expectant management under regular monitoring	Women with pregnancy induced hypertension or mild preeclampsia with a gestational age of 34 - 37 weeks of gestation
Ppromexil[14]	What is the effectiveness and cost-effectiveness of induction of labor after PPROM between 34 and 37 weeks gestation compared to expectant monitoring?	Induction of labor or expectant monitoring	Pregnant women with preterm premature rupture of membranes between 34 + 0/7 weeks to 37 weeks of gestation
ProTWIN[16]	Is prophylactic use of a cervical pessaryeffective in the prevention of preterm delivery and the neonatal mortality and morbidity resulting from preterm delivery in multiple pregnancy?	Pessary or no treatment.	All women presenting with a multiple pregnancy between 12-20 weeks of gestation
WOMB[13]	What is the effect of RBC transfusion on health related quality of life?	RBC transfusion or no intervention	Women with HPP or a decrease in Hb, 12 to 24 hours after delivery or caesarean section

*More information about these studies can be found at: www.studies-obsgyn.nl

All interviews were recorded and transcribed. Participants were asked for verbal consent for audiotaping, after verbal consent was given the audiotape was started. We informed the women that whenever they felt uncomfortable during the interview, they were permitted to stop the interview at any time, even for no reason.

The transcript was sent to the interviewees to confirm correctness and completeness (member-check). If the women indicated that the interview was not a good reflection of their motives or they did not want their information to be used any longer, the information was not used. All transcripts were coded using one letter of the alphabet, with the code only know to the interviewer and transcriber (SL and KOR). Transcripts were not shared with their treating physician. We estimated that an interview with about 10 women in both groups would be needed to reach data saturation, based on previous papers published (8). We planned to perform two additional interviews when data saturation was reached.

Analysis

The aim of the analysis was to group the content of the interviews into main themes. Analysis was performed according to the taxonomy of Strauss & Corbin ('create theory out of data'), where one starts with line-by-line open coding of all relevant phrases of barriers or motivators for participation (open coding), using a constant comparison method: newly gathered data are continually compared with previously collected data and their coding, in order to refine the development of theoretical categories (18).

After open coding, the codes were grouped into categories (axial coding), and then into themes (selective coding)(18). All transcripts were reread and recoded, using the refined coding structure. A fragment was placed into all relevant categories. Two researchers (SL and KOR) independently analysed the first seven interviews, thereafter one researcher marked barriers and facilitators, which was checked by a second researcher. Discussion was resolved by consensus if needed. For the purpose of this article direct quotes from the interview were translated by a professional translator, after analyses had been finished.

RESULTS

Interviewees

Of the 28 identified women, four women could not be reached by phone, two non-participants declined an interview, and one woman initially consented but was admitted to hospital for emergency care. Her interview was cancelled. Twenty-one interviews were performed (12 with trial participants and nine with non-participants), of which 17 were face-to-face interviews and four were by phone.

The interview took on average about half an hour. After transcription of the recorded interview, 20 interviewees approved its content, while one woman did not respond. Characteristics of the interviewees are shown in Table 2.

Table 2. Characteristics of the women included

Code	Ethnicity	Level of education	Age	Study	Parity*	Place	Hospital
	Participants						
J	Dutch	Intermediate/low	30	Allo	0	Veldhoven	MMC
L	Dutch	Higher education	39	Allo	1	Veldhoven	MMC
M	Dutch	Higher education	34	Allo	1	Veldhoven	MMC
N	Dutch	Higher education	29	Apostel I	2	Veldhoven	MMC
P	Dutch	Higher education	28	Ppromexil	0	Enschede	MST
Q	Dutch	Intermediate/low	26	Ppromexil	0	Enschede	MST
T	Dutch	Higher education	32	Hypitat II	1	Amsterdam	OLVG
U	Dutch	Higher education	39	ProTWIN	0	Amsterdam	OLVG
V	Surinam	Higher education	38	Hypitat II	2	Amsterdam	OLVG
W	Dutch	Higher education	36	Apostel II	2	Amsterdam	OLVG
Y	Surinam	Higher education	37	CHIPS	1	Amsterdam	OLVG
Z	Belgian	Higher education	29	WOMB	2	Amsterdam	SLAZ
	Non-participants						
A	Dutch	Higher education	35	WOMB	1	Amsterdam	SLAZ
B	Dutch	Unknown	27	ProTWIN	0	Amsterdam	OLVG
C	Dutch	Higher education	34	ProTWIN	1	Amsterdam	SLAZ
D	Moroccan	Higher education	33	ProTWIN	1	Amsterdam	SLAZ
E	Surinam	Higher education	39	Hypitat II	1	Amsterdam	AMC
G	Dutch	Higher education	27	Apostel II	0	Amsterdam	OLVG
I	Dutch	Higher education	22	ProTWIN	0	Enschede	MST
K	Dutch	Intermediate/low	22	Ppromexil	1	Veldhoven	MMC
O	Dutch	Intermediate/low	23	Hypitat II	0	Veldhoven	MMC

*Parity was registered at the time of the interview

Five women had been invited for this study more than three months after being invited to a trial, mostly due to incomplete registration of non-participants. All respondents stated they remembered the situation that was discussed in the interview very well, which we confirmed during the interviews. We considered data saturation reached, as no new motives were mentioned during the last two interviews. As we sampled participants from different studies, we defined data saturation as no new motive emerging over all studies. For example, we considered 'distrust in the effectiveness of a new intervention' as a motive, whether this was a pessary in the Pro Twin trial or iron tablets in the Womb study.

Main motive for trial participation or non-participation

The main motives for trial participation as mentioned by the women are shown in Table 3. Contribution to scientific research was for 5 of the 12 participants the main motive for participation in the trial, sometimes conditional upon other motives (J, L, T, U, Z). Five participants mentioned to have participated because the intervention seemed favourable and was not available outside the trial (M, P, Q, V, W). One woman thought an extra test could only positive effects, as '*there is no harm in trying*' (N). For one woman the reason was not very clear, she most probably meant to be better informed about her medical condition (Y). Key reported motives for the 9 non-participants were a negative association or dislike of one of the interventions, either because it might do harm (C, D, E, G, I, K) or for practical reasons associated with the intervention (A, B, O). Women also described first-time pregnancy or being in an exceptional situation as playing a role, or she was already in a in an exceptional situation, like a twin pregnancy or a pregnancy after intrauterine insemination.

Table 3. Main motives for participation or non-participation as answered to the starting (open) question

Code	Citation
J	"I don't think research is ever actually bad, and this is not a study where they do real experiments, so it's always good to learn from it for someone else."
L	"Actually, in our first pregnancy our daughter was in foetal distress and so we had to have a caesarean section. This might have been an option then, too, as it has something to do with foetal distress, then administering this. And my husband actually asked more questions: does it have drawbacks for the child? No? Then we'll join, because the study is necessary. There's also my medical background. I've worked on maternity wards, too. When you work in medicine, you're open to innovation and new techniques."
T	"Two things, actually. In my first pregnancy I had pre-eclampsia, so I was very well aware what the consequences might be for me, and then also for the child… Personally, I support the aims of the study, to let you have your baby from 34 weeks onwards, because the risks do not outweigh for mother and child, so to speak. Second, I've been coming to a teaching hospital for years, for other treatments as well, and I believe very much in the academic side. I believe in development and trying new things. And, well, research is part of that because if you never do any studies, you can never do anything new."
U	"Well, originally I was invited to take part in a study about the pessary, a study of twins. I thought: seems good to me, I have a twin sister myself and I used ICSI to conceive, so there were also people who took part in this kind of study for me. That's how I'm pregnant now."
Z	"Well, first, it did really apply to me and there was the choice between taking blood or iron. Otherwise it would have been iron, whatever. So I thought, let's see what happens with this. And I was in the blood group. Looking back, I'm very happy with it. And, as I just said, I often do studies myself. So then you know better how important it is, that you need to recruit people, so eh, actually that's the only reason."
M	"The most decisive factor, of course, is that the consequences of oxygen deprivation are pretty severe. If you could reduce that in some way, by taking a particular drug, then I'd choose it. Yes, yes, good. And because the drug was already being used for other things – OK, so it hadn't yet been fully tested for oxygen deprivation – then it shouldn't have any bad effects. You assume that it can only be beneficial. And so then I think, like, that's something I want to take part in."
P	"OK, well, that was mainly due to the fact that there was a chance that my labour would be induced, otherwise I'd have to wait until 37 weeks come what may…The contribution to research as well, of course, I thought that was a good cause, but it wasn't the most important. I thought: I'm going for immediate induction. I couldn't imagine having to stay in hospital for five days, not allowed to do anything, so I thought, like, let it come now."

Table 3. Main motives for participation or non-participation as answered to the starting (open) question (*continued*)

Code	Citation
Q	"First of all, I don't see myself lying here for another five weeks. And pretty soon after that the realisation that you're already open down there, with a risk of infection for yourself and for the baby. And yes, in Enschede the doctors also said it was viable enough, so that was for us a reason to take part."
V	"That once the baby was out my high blood pressure would be gone. That's what I thought, that was about it. But on the other hand, I was a bit scared. Will I have him earlier – that was at 36 weeks – so it was a bit of a dilemma deciding what would be best. Then she explained to me: the earlier the baby's out, the better it should be for mother and child. So that was actually the reason why I said I'd do it."
W	"That was because I hoped it would be better for the baby, although I still had an uneasy feeling about it. That was because nobody could say what the potential adverse effects were. Yes, I kept on feeling uneasy about it."
N	"And I thought something like, in my case it can only be positive because, I mean, the test would indicate whether the chance was very high that you would deliver very soon, or that it could take a while. So I really felt like I wasn't running much risk, because if the test showed that you fell into the test group, then you would get either a placebo or tocolytics."
Y	"Then you know how and what."
C	"Well, there were several reasons actually. When your colleague started talking about it, when I had an appointment about it, I thought: 'Oh my God, no, not a pessary! Because I had a friend who was admitted to hospital because a pessary [not in pregnancy] had caused a lot of bleeding. So that's what I told her [the colleague]: that that had been a life threatening situation. So I had a feeling of, like, if I think now about pregnancy and a pessary, it doesn't make me very happy."
D	"For me it was pretty clear, actually. Once I was here I thought, like, just let Mother Nature do her work. I'm pretty religious [Muslim], so perhaps there's a reason why those children are born early. I believe in God, you know. I think, like, fate decides. If those children want to be born earlier, then so be it. If not, then not. That was my thinking. I was scared, too. What if I take part and something happens to me, a bit of blood loss – or a lot – or something happens to the babies."
E	"She [baby] was four weeks early and that blood pressure kept on rising. They just couldn't get it down. I'd already been lying there for a month and I'dhad enough. You want something to happen. Then they asked me: do you want to take part in this study? Because there'd come a point when the doctors were saying, we don't know any more, either. So I thought, well, if they don't know, who does? I had to make my own choice. ... And then I thought, actually I can better prolong it for a while, to see how long it takes. Because if I had decided to take part, you don't know whether you'll be induced or not. That's not certain, either. So then the disappointment can be huge. That was when I decided not to do it, to see how long we could prolong it."
G	"I had a very tough pregnancy, with a lot of bleeding, and in fact the whole nine months were entirely uncertain… I was given those lung development injections and tocolytics, after which I couldn't feel my baby at all… When they asked if I wanted stay on the tocolytics, I linked them a bit with that so I thought, like, no – because I wanted to feel my baby again as soon as possible, to regain a bit of the certainty that everything was alright. So for me, that was the most important reason."
I	"At first I was really inclined to participate, because a lot of people close to me said, just say it works. Your babies will stay inside longer. But personally, I had the feeling that everything was going very well, that it all, yes… And I do react quite strongly to things, to jewellery or a piercing or something. So I think, if something's going to be stuck inside my body, it might react really badly. If nothing's wrong and I do that… I found that a bit scary. And then there's the fact that you couldn't choose which group you were in. That's logical with a study, but that's why I didn't do it in the end."
K	"Well, it's not without a reason that they tell you that you're officially allowed to deliver from 37 weeks on, so yes, I thought it was a risk being induced at 34 weeks. Because the doctors don't just say: from 37 weeks the doctors will induce you automatically and they're doing a study and I didn't want to be a guinea pig. If something then goes wrong …"

Table 3. Main motives for participation or non-participation as answered to the starting (open) question (*continued*)

Code	Citation
A	"I would happily have taken part if I could have opted for iron tablets, but that choice wasn't available. You have to participate blind, and then I don't know who decides. I don't know how that works, but someone else decides for you which of the two you are going to do. What's also complicated: I didn't want a blood transfusion. I was lying there on a drip and I had a catheter, and then I thought that with iron tablets I could go home and otherwise I would have to stay even longer."
B	"I'm at the AMC. That's a teaching hospital and they do all kinds of research there. I would have to come in more often – it was all about a pessary against premature birth – and I would have to come in more often to measure it up and for ultrasound. I did seriously consider it, but those extra visits… If I was in pain, for example, or it wasn't convenient. And I'd just heard I was pregnant with twins sharing an amniotic sac, which is a very rare situation – you have a lot information coming at you."
O	[Unplanned pregnancy] "Yes, and everything suddenly went so fast. Then I really thought, like, well, I don't have to be induced tomorrow. That… the chance was 50 percent, and I didn't need that. No, I feel it's all gone too fast. Because you're… No… After three weeks attending the hospital, I was admitted. I'd never been in hospital before and… Yes, yes, I was homesick. Yes. But, I didn't think, like, whip him out tomorrow. Really, that just wasn't what I wanted. That was simply too fast for me. I couldn't take it all in."

Themes identified as related to the decision on trial participation

During the open coding we identified 47 sub-codes, based on phrases relating to barriers and facilitators. These were grouped into 13 categories, and further grouped into seven main themes (Table 4), discussed below.

Table 4. Seven main themes that influences trial participation

Theme	Sub codes
External influence	§ Concern from social environment § Trust in the health professional § Feeling of disappointing the health professional
Research and healthcare	§ Familiarity with scientific research § Willingness to contribute to research § Feeling of participating in an experiment
Perception own situation	§ Perception own situation and medical history § Feeling very eligible or very ineligible for scientific research
Study design	§ Randomisation § Blinding § Placebo § Additional efforts § Insurance medical research
Intervention	§ Intervention § Natural course
Information and counseling	§ Written information § Counseling: information and timing, atmosphere § Time for consideration on participation
Uncertainty	§ Fear § Stress § Doubt § Physician does not know what is best

A. External influence

Women indicated that they discussed the invitation to enroll in a trial with their partner, where the partners opinion influenced the decision on whether to participate or not. This influence could be either positive or negative, giving the women more confidence to decide to participate or withholding her from participation if the partner perceived more risks of participation. In the two cases the woman and her partner disagreed. Women indicated that opinions of persons other than their partner were not very influential.

> *''I did discuss it with my husband. I thought, like, if it would have been only my decision, I would have agreed to participate. My answer depended on my husband's opinion. He thought it was a good decision, so we unanimously agreed on participation. Interviewer: ''What if you partner had disagreed?'' Participant: ''Then I would not have participated in the trial.'' (Participant Allo trial)*

Women indicated they had decided on participation without consulting their gynaecologist, however when the gynaecologist was contacted, his or her opinion was in most cases influential. All respondents felt free to make their own decision, without feeling pressure from anyone to participate.

B. (Contribution to) research and healthcare

Contribution to scientific research was a reason for participation, as they were convinced about its importance.

> *"I reasoned also, like, these are studies for the future, and I have a daughter, and you never know… I am prepared to participate for others, so things will be better in the future than how they are now. I am benefiting from what others have done before me." (Participant Hypitat II trial)*

Interviewees who had declined participation judged scientific research also important, but other themes outweighed this importance. One participant suggested to improve publicity on clinical trials and research in pregnancy:

> *"Maybe one should increase the awareness about the existence of studies one can participate in in case of pregnancy. Maybe, somehow, more people should be informed once pregnant, so they know about trial participation. Myself, I did not think about it - I have not experienced this before. I think receiving a folder with 'scientific research for pregnant women' in advance would decrease the level of stress. If you had read it, you would know it might be coming up. So one can already think about research." (Participant Ppromexil trail)*

C. Perception of one's own situation

The personal perception of one's own situation appeared influential in the decision on participation: women considered themselves either very eligible or not at all eligible for scientific research, sometimes taking into account their current complicated pregnancy, medical history or their own nature.

> *"There are people who participate in trials; that is very special and good, but I am not such a person, all that twiddling to my body. Maybe I would if it had been a singleton pregnancy, but now, with twins, it is already scary: and all the twiddling to your body. I prefer nature." (Non-participant ProTwin trial)*

Intuitional or emotional elements were also reported. When asked whether their decision was rational, some women answered they trusted their feelings, or were inclined to participate but did not participate because it did not feel good.

D. Trial design

Randomisation was perceived negative and resulted in uncertainty. Women could not explain (in any way) why randomisation was used, or could be used. This seemed based on a combination of not knowing why randomisation could or should be used, and not trusting that there is really equipoise and the doctor does not know what is the best for them. In the Netherlands, when explaining randomisation as 'loten' a Dutch word meaning drawing straws that has the connotation of faith or destiny, this was perceived negative, while explaining randomisation by means of a computer selecting a group for the participant, this was considered more positive. Therefore Dutch doctors should avoid this. However this lack of knowledge was not necessarily a barrier for participation.

> *"If I had decided to participate, there would be uncertainty about induction. So the disappointment can be huge. No, with the uncertainty you don't know if you take a left or a right. If you decide yourself, you know where you go. You now: I go right." (Non-participant HYPITAT II trial)*

E. Intervention

Participants mentioned the potential therapeutic benefit of the intervention as a reason for participation.

> *"Well, if in this case, if they stay in longer, that's an advantage for me as well. That was actually the only reason to participate. But I needed to be convinced that there were no disadvantages, that it was not detrimental if they stayed in shorter, because of that." (Participant ProTwin trial)*

Other women disliked an interventional ("active") strategy, and rather preferred the natural course, or were more focused on potential (unknown) negative effects. They mentioned that the risk associated with a natural course is one you do not choose for. It is already present, contrary to the risk of an intervention or the risk of trial participation, which result from the women's choice. All non-participants stated that a negative association with the intervention or a negative effect of intervention played a role, as discussed under the main motivations.

> *''They were uncertain about side-effects for the baby, so then I decided not to take any risk. To me it was already pretty clear: during my time here, I wanted to let mother nature take its course. I am not going to mess with it. If nature decided it to be this way, I let it be, you know.'' (Non-participant ProTwin trial)*

F. Information and counseling

Women considered the information adequate, but indicated that the counseling was done very hastily. A no rush atmosphere, where counseling was often done by a research nurse or midwife, with sufficient time to discuss patients questions, was viewed as positive.

> *"Thinking back, I realized it matters a great deal who comes to inform you about the study. Imagine a research midwife is standing at my bed, taking the time, versus a doctor is sitting at the windowsill, just not looking at her watch, saying "I have 5 minutes, so you have to decide now, otherwise it will be too late." That makes a difference, and influences the outcome of the decision." (Participant Apostel II trial)*

One women said she had received unclear and incomplete written information, but nonetheless she participated.

> *"I only understood later that these were the same tocolytics as you would receive usually, there is nothing different about. It is not a new medication, that's what I understood later. That was unclear at the time I had to decide, it seemed if it was a new medication, with a new method to look at whether the baby would stay in longer with premature rupture of membranes and what the harmful effects for the child or the mother would be. If they had explained it better, had told me what the potential adverse effects were - that is of course the point of the trial -than it would have been easier to participate. If they had only said something like "the only potential harmful effect is that you baby may be a bit smaller, or bigger, or more left, or right" but it's quite difficult if you don't know. It's an ethical dilemma." (Participant Apostel II trial)*

Women felt the time to consider participation was adequate, or they understood why the time for consideration was short, except one woman. Some women declined participation because there was an overwhelming amount of new information, or timing was not right.

G. Uncertainty

The theme uncertainty emerged in interviews of both participants and non-participants. Non-participants explicitly mentioned to have declined participation because of feelings of uncertainty. This prevailed over other factors even before they had reached the stage explicitly weighing advantages and disadvantages on participation.

> *"No, I did not consider that, I did not think about it. For me the safety of the baby was most important. No, I did not see an advantage. No, that 'advantages aspect', they [the doctor/counsellor] did not talk about it. And I did not ask for it." (Non-participant Ppromexil trial)*

In both groups women indicated that being confronted with an (unexpected) invitation to participate in scientific research the invitation to participate in scientific research was stressful and needed thorough consideration.

> *''Whether it is really stress, I am not sure, we have talked about it a lot, both my husband and I, and also with a friend of mine who lives in Rotterdam. It was also on my mind quite a lot, but whether it has caused me physical stress, I am not sure. Yes, I have thought a lot about it, as one never seems to make the right decision. If he had been born, and something had been wrong, while I had not participated, I would have wished I had. On the other hand: if I had participated in the trial and something had gone wrong, I would have wished not to have participated in the trial.'' (Participant Apostel II trial)*

Some of the women were really surprised when confronted with the fact that '2010 state of the art health professionals' do not know what treatment is best.

> *"They [the doctors] said "We think it is silly to say - and may sound very strange to you - but we have to be honest: we don't know". And I was lying there and thinking all the time "I'll see what happens" until that moment. Then I thought "I feel left to my fate". I thought it was very honest, but also very hard. You are there for a reason, and they are supposed to know, they have studied for this. I assumed they could tell me in what direction to go, but that, they could not. That is really tough. They could only provide me with certain facts, that neither actually, and the research was there for a reason.'' (non-participant HYPITAT II trial)*

DISCUSSION

Contributing to scientific research was for many participants their main motive for participation in the trial, while others were motivated to participate because the intervention seemed favourable and was not available outside the trial. Key motives for non-participation were a negative feeling towards the intervention, either because it might do harm or for practical reasons. We identified seven themes that influenced the decision to participate in a trial. We noted that uncertainty about scientific research or the intervention was of considerable importance.

This study examined a variety of trials, which were not selected based on their recruitment performance. We sampled patients from multiple trials, multiple centers, invited to enroll by various health professionals, in different geographical areas in the Netherlands. The response rate was high. More non-participants declined an interview, however only two of eleven non-participants invited by phone declined to be interviewed. All interviewees stated that the counseling and the decision making process were very well remembered, which was confirmed by the interviewer. Therefore, we think this did not very much influence the reported barriers and motivators. The varying settings of the interview – either at home or in the hospital – could have influenced the results. As we left the choice for the setting to the interviewee, we think the interviewees had chosen the setting where she felt most comfortable to talk about their decision. Most interviews were at the woman's home. We felt the setting did not restrict women to talk openly about their motives for or barriers to trial participation.

A potential limitation of qualitative research is the introduction of bias, as interpretation is an inevitable part of the analysis of the transcripts. We therefore relied on two researchers to examine the transcripts. Another limitation is the relatively small sample, were we included a high rate of women with higher education. However, views of women with lower or intermediate education were represented. Moreover, in the group of participants more women seem to be multiparous and older than in the non-participants group. A possible explanation for this, is because they are more familiar to being pregnant and they already delivered before, and therefore multiparous women more often participated. However, given the small sample we cannot exclude that these differences are due to chance.

We considered the sampling of women over multiple studies as a strong point of our study, improving generalisability, but given the small sample it is difficult to determine the effect of the sampling from the different studies on the reported barriers and facilitators. This has affected the relative importance of the different barriers and motivators, but this study was designed to get an overview of the main aims for participation or non-participation in trials.

We considered data saturation reached, defined as no new information emerging during the last two interviews. However, the interpretation of data being saturated could be argued. As we sampled from different studies, we considered 'distrust in the intervention' as a motive, whether this was a pessary in the Pro Twin study or iron tablets in the Womb study. We think this was adequate for getting an overview of the reasons to participate or not participate, but

adding more studies might lead to more variety within the motive 'distrust in the intervention'. In order to quantify or to determine the magnitude of the results in the total population, a larger cross-sectional survey in a representative group of women should be done.

The seven themes identified in this study have been reported previously. Kenyon et al. conducted interviews with women who had participated in the ORACLE study, a randomised trial investigating the value of administration of antibiotics during premature labour. They concluded that women gave prominence to the socio-emotional aspects of their interactions with healthcare professionals in making decisions on trial participation. The interviews suggested that the stressful situation (of being asked to participate in a trial) affected their ability to absorb the information. The main motivation for trial participation was the possibility of an improved outcome for the baby. Another important motivation was an opportunity to help others, but this was conditional on there being no risks associated with trial participation (19). McCann and colleagues introduced the term 'conditional altruism', which describes that the willingness to help others initially inclines people to participate in a trial, but is unlikely to actually lead to trial participation unless people also recognize that participation will benefit them personally (20).

Uncertainty due to unfamiliarity with research or research methods was also identified as a theme related to trial participation in pregnant women (6,21) and in a systematic review not restricted to pregnant women (21). Unfamiliarity with randomisation was a reason for uncertainty; for many patients it remained unclear why randomisation is used. Robinson and colleagues investigated lay public's understanding of equipoise and randomisation in hypothetical randomised trials (22). Even participants who could correctly explain the rationale behind random allocation doubted the possibility of individual equipoise and saw no benefits of random allocation over the doctor/patient choice. They concluded that, given the extent of disparity between the assumptions underlying trial design and the assumptions held by the lay public, the solution is unlikely to be simple.

Some women reported that they would let mother Nature do her work. They were reluctant to actively choose for an intervention in an (perceived) uncomplicated pregnancy. Lyerly at al. reported that women focused on risks associated with medical interventions during pregnancy, not taking into account the demonstrable risk to both woman and fetus of not intervening (23).

Many women were surprised to learn that the doctor does not always know what is best. This was also reported by Mohanna: 'Some patients will prefer to assume that [*My*] doctor knows best [*about me and my baby*], and are not happy to enter into the discussion of uncertainty that a trial and the issue of informed consent will raise' (24). Counseling by research staff, instead of the treating physician, seemed to influence participation positively, which has also been suggested in the review of Tooher and collegues (7).

To reduce feelings of uncertainty and stress, further research could elaborate on the work by Junghans and colleagues, where an opt-out design for low-risk interventions was proposed (25,26). This could not only increase participation rates, leading to a more representative study group, but might also shift the responsibility and difficult decision process from pregnant women

to the health professionals. Ethical committees could or should be responsible for identifying low-risk trials eligible to run in this system. Patients could for example be informed about this general policy of opt-out consent when entering the hospital, invited to sign a general informed consent about the use of data to improve quality.

Alternatively, one could think of a trial classification system, where the potential risks of a trial are communicated with uniform labels, much like energy labels, to make them more transparent for patients. An "A" classification for example could mean that widely used interventions are compared, with no additional risk compared to usual clinical practice. A classification of "E" could mean that the new intervention being tested is highly experimental. One could imagine that health professionals generally recommend participants to participation in all "A" trials, instead of explicitly leaving the choice to the patient.

Uncertainty could also be reduced, and awareness improved, if pregnant women become more familiar with scientific research in general, and studies in pregnancy specifically. This calls for a national public campaign. In 2008 the 'Get Randomised' campaign was launched in the UK, informing the public about the importance of clinical trials using television, radio and newspaper advertising. The campaign increased public awareness of clinical trials, but those who did recall the ads were not more inclined to personally take part in a clinical trials if invited, than those who did not remember (27). In the United States a comparable campaign celebrating the 'everyday medical heroes' of clinical research has been established. Its initiators believe the public has a poor and often negative understanding of clinical research (28).

For trials in pregnancy, general information leaflets, available when entering a midwifery practice or a hospital, could introduce the goals, methods and necessity of scientific research. Health professionals could discuss trial participation in general, and trials in pregnancy in specific, early in a pregnancy. Or a national public campaign that raises awareness and reduces barriers to participation in trials could be considered. All this could habituate women more to scientific research and methods used in it.

CONCLUSION

We identified seven themes that influenced the decision to participate in a trial. Contributing to scientific research was for many participants their main motive for participation in the trial, while others were motivated because the intervention seemed favourable and was not available outside the trial. Key motives for non-participation were a negative feeling towards the intervention, either because it might do harm, or for practical reasons. We noted that uncertainty about scientific research or the intervention was of considerable importance. Measures should be taken to habituate pregnant women more to scientific research and the methods used in it. Without pregnant womens' contribution and participation, we would not be able to advance our understanding of the effectiveness of interventions in pregnancy and childbirth.

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ADDITIONAL FILE

Appendix 1. Topic list

Openingsvraag: Wat deed u besluiten om wel/niet mee te doen aan het <*trial acronym noemen*> onderzoek?

De originele topiclijst zag er als volgt uit. Gedurende het onderzoek zijn enkele topics verwijderd en een aantal nieuwe topics toegevoegd.

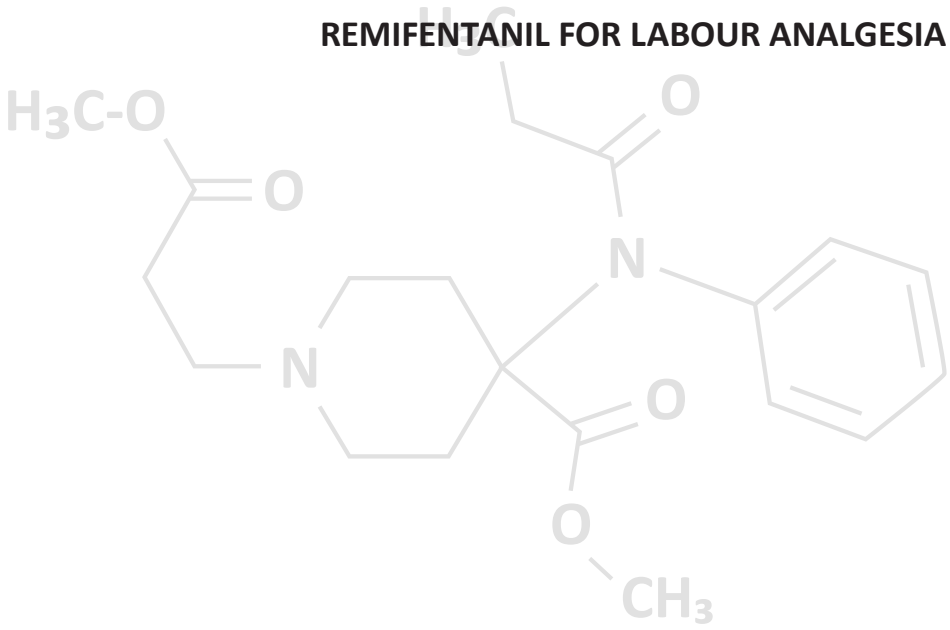
Topics:

- *Persoonlijk voordeel:* therapeutisch voordeel bij deelname, meest recente therapie, voldoening, meer/betere monitoring van ziekte, betere relatie met behandelaar, vrijheid
- *Onbaatzuchtigheid:* bijdrage wetenschap, behandelaar een plezier doen, andere patiënten met deze aandoening helpen
- *Kennis/informatieverstrekking:* precies weten waar je voor kiest, elk moment kunnen stoppen, randomisatie, placebo, geblindeerd onderzoek/dubbel blind onderzoek, doel van de studie, patiëntinformatie
- *Bezorgdheid/wantrouwen:* nadelige gevolgen behandeling, bekende behandeling beter, (extra) injecties/medicatie, bezorgdheid informed consent, angst voor onbekende, verlies controle, inbreuk privacy, studiedesign, stress
- *Organisatorisch:* afspraken, bedenktijd, extra consulten/injecties, reistijd en kosten, werk, kinderopvang, tijd voor "onderzoeks consult"
- *Attitude*: houding ten opzichte van wetenschappelijk onderzoek
- *Sociale omgeving:* invloed partner/omgeving/internet, wie maakte keuze, behandelaar niet enthousiast over studie, verplichting ten opzichte van behandelaar, moment van counseling

CHAPTER 9

Summary & discussion

REMIFENTANIL FOR LABOUR ANALGESIA



SUMMARY

This thesis explores questions about remifentanil patient controlled analgesia (remifentanil-PCA) for labour analgesia. The thesis aims to contribute to the place of remifentanil-PCA for labour analgesia, both from the perspective of women and health care providers. We studied questions concerning the satisfaction of women, the association with fear of childbirth and the safety, the availability and the appropriateness of remifentanil-PCA for labour analgesia. In addition we studied the challenge of recruiting pregnant women for participating in clinical trials from the perspective of pregnant women.

Chapter 1 presents a general overview of labour pain, (non-) pharmacological pain relief and what is known about remifentanil-PCA for labour analgesia. In this chapter the objectives and the research questions for this thesis were introduced.

Chapters 2 & 3 report the results of two randomised controlled trials - RAVEL- comparing two methods of pain relief in women with a low or an intermediate to high obstetric risk. Equivalence could not be demonstrated for remifentanil-PCA with respect to satisfaction with pain relief compared to epidural analgesia assessed during the total time of labour, both for the low and the intermediate to high obstetric risk group. Once applied satisfaction with pain relief was higher in women who received epidural analgesia. Since in many settings remifentanil-PCA is more readily available than epidural analgesia, it can be an alternative for pain relief during labour.

Chapter 4 presents the results of a secondary analysis of the RAVEL study looking at the association between fear of childbirth and pharmacological pain relief in women with a low obstetric risk. Women with fear of childbirth antepartum more frequently requested pain relief, but this association did not reach statistical significance. Women who received pharmacological pain relief reported more frequently fear of childbirth postpartum. When looking at fear of childbirth postpartum, epidural analgesia with continuous infusion does not seem to be preferred over remifentanil-PCA as method of pain relief.

Chapter 5 describes the results of a survey among gynaecologists in all 81 Dutch hospitals with a labour ward to assess the current use of remifentanil-PCA in Dutch labour wards. A large variation between hospitals exists in the use of remifentanil-PCA for labour analgesia, varying from 0 to 56% of all deliveries. In the majority of the hospitals, remifentanil-PCA is available for all women despite restrictions of the Standard Operating Procedure (SOP) for remifentanil-PCA. Most reported considerations for the administration of remifentanil-PCA are **'**need for an alternative for epidural analgesia' and 'at the request of pregnant women'.

Chapter 6 reports the result of a survey among gynaecologists, anaesthetists and clinical midwives to examine the number of serious adverse events (SAEs) attributed to remifentanil-PCA use for labour analgesia. We found ten maternal cases of apnea; bradycardia and/or cardiac arrest and two neonatal cases of respiratory depression over a period of more than ten years of

remifentanil-PCA use in The Netherlands. All patients with SAEs recovered completely without deficit at the end of treatment. Although the risk for an SAE seems to be low, the adherence to strict maternal monitoring during remifentanil-PCA and the attendance of trained healthcare providers are essential to safely use remifentanil-PCA.

Chapter 7 presents the results of a secondary analysis of the RAVEL studies. We investigated whether we could identify women with a request for pain relief who would be as satisfied with remifentanil-PCA compared to epidural analgesia. We developed and internally validated a multivariable treatment selection model for satisfaction with pain relief during labour. The model contained treatment and the following variables: education level, gestational age, previous vaginal delivery, ethnicity, risk category, antepartum fear of childbirth score, BMI, augmentation with oxytocin, dilatation, as well as a treatment - ethnicity interaction and treatment - risk category interaction. Our model identified 18,3% of the study group as women who would be satisfied with remifentanil-PCA. After external validation this model could be used to guide decisions about remifentanil-PCA for labour analgesia.

Chapter 8 describes the findings from 21 semi-structured interviews with pregnant women - invited to participate in a randomised clinical trial - on their motives whether or not to participate during their pregnancy. Contributing to scientific research was for many participants their main motive for participation in the trial, while others were motivated because the intervention investigated seemed favourable and was not available outside the trial. One of the key motives of pregnant women for non-participation was a negative attitude towards the intervention, either because it might do harm to the mother and/or the fetus, or for practical reasons. We noted that uncertainty about scientific research or about the intervention was of considerable importance.

GENERAL DISCUSSION

Labour pain

Labour pain is generally considered as very severe pain. Women's experiences of labour pain and the way labour pain is managed vary greatly and are influenced by internal and external factors (1). Management of labour pain differs worldwide depending on e.g. cultural background and care practices and changes over time (2,3). There is a variety of non-pharmacological and pharmacological methods of pain relief, either to encourage a physiological birth process and/or to relief labour pain. Continuous support of labour is, regardless of the care setting, either midwife-led care or hospital-based obstetric-led care, probably the most important intervention to aspire a process of childbirth as physiological as possible. It improves childbirth satisfaction and it is preventive for (unnecessary) medicalisation (4). Despite a policy for continuous support of labour there is –worldwide- an increasing group of women requesting pharmacological pain relief during labour (5). For each woman who requests pain relief the question arises

which method of pain relief is the most suitable method. This thesis provides information to make a thorough decision on the place of remifentanil-PCA as an appropriate method for pain relief during labour and for the counselling of pregnant women.

Remifentanil-PCA

Experiences with remifentanil-PCA compared to epidural analgesia

In both RAVEL studies (chapter 2 and 3) we could not demonstrate equivalence between the remifentanil-PCA and epidural analgesia, although we found comparable satisfaction with pain relief during the total period of labour of women in the remifentanil-PCA and the epidural group. However, after the start of analgesia satisfaction with pain relief was lower in the remifentanil-PCA group than in the epidural analgesia group. Volmanen et al. and Douma et al. found comparable satisfaction scores with remifentanil-PCA and with epidural analgesia (6,7). Both studies had limitations such as satisfaction being a secondary outcome measure and an observation period of only one hour. In both RAVEL studies pain intensity scores were higher in the remifentanil-PCA group than in the epidural analgesia group; this is in accordance with previous studies and with a recent Cochrane review of Weibel et al. (1,8). Although remifentanil-PCA gives lower satisfaction with pain relief and higher pain intensity scores, it has the advantages of the availability without the attendance of an anaesthetist and it can be provided even at the end of the first stage of labour. Besides, it is known from clinical practice, the RAVEL studies, and the study about practice variation (chapter 5) that there is a group of women with a preference for remifentanil-PCA instead of epidural analgesia. Although probably most women prefer the most effective method of analgesia, some women may prefer a less invasive method with a lower level of pain relief. For these women remifentanil-PCA may be considered.

In the RAVEL studies we did not find a difference in assisted vaginal birth rates between women randomised for remifentanil-PCA and women randomised for epidural analgesia. This finding is analogue to Weibel et al. who found in a Cochrane review no differences between assisted vaginal birth for women using remifentanil-PCA or women using epidural analgesia (8). Previous research reported that women using epidural analgesia during labour are more likely to have an assisted vaginal birth instead of a spontaneous vaginal birth (9). We doubt if this effect is strictly associated with the use of epidural analgesia itself or whether it is, at least partly, confounded by the indication for pharmacological pain relief. A request for pharmacological pain relief maybe indicated by a failure to progress in labour or by the experience of very severe labour pain already in the latent phase of labour. Probably women in these situations are – even without epidural analgesia - at risk for an assisted vaginal delivery on the basis of abnormal progress of labour. Besides, the recently updated Cochrane review of Anim et al. on this subject did not show an increased risk for assisted vaginal birth in a subgroup analysis of recent studies after 2005. This could be the result of the current management of labour during epidural analgesia (10).

Remifentanil-PCA and fear of childbirth

In a secondary analysis of the data of the RAVEL trial among low risk women we focused on women with fear of childbirth (chapter 4). Women with fear of childbirth usually more often request pain relief than women without fear of childbirth (11,12). We compared our results with previous literature in which fear of childbirth was usually investigated in women with a mixed obstetric risk, that is both women with a low, and women with an intermediate to high obstetric risk. The frequency of fear of childbirth antepartum and fear of childbirth reported postpartum in low risk women we found was comparable with the literature (13–15). In accordance with previous studies we found that women with fear of childbirth antepartum were more likely to request pain relief compared to women without fear of childbirth, although our results did not reach statistical significance. The finding that women who received pharmacological pain relief more frequently reported fear of childbirth postpartum is also analogue to earlier studies (14,15). Fear of childbirth postpartum occurred in our study more often in women who used epidural analgesia compared to women without the use of pain relief. We did not find a significant association with fear of childbirth postpartum for remifentanil-PCA. The result that fear of childbirth antepartum is cogent related to fear of childbirth reported postpartum is consistent with previous studies (15–18).

Practice variation and serious adverse events in The Netherlands

Obviously, to create a thorough picture of the role of remifentanil-PCA as labour analgesia insight in the use of remifentanil-PCA and the number of serious adverse events (SAEs) attributed to its use are of importance (chapter 5 and 6). We found that remifentanil-PCA was applied 21,000 times per year both in 2016 and in 2017 in The Netherlands as labour analgesia. These results substantiate the assumption of The Dutch Health Care Inspectorate in 2013 that remifentanil-PCA was widely used as labour analgesia and it implies that a substantial part of labouring women chooses for remifentanil-PCA as labour analgesia.

One of the main motives for gynaecologists to offer remifentanil-PCA was 'at the request of pregnant women'. However, the Standard Operating Procedure (SOP) for the use of remifentanil for labour analgesia indicates that there can never be a free choice between remifentanil-PCA and epidural analgesia for the patient. According to the SOP the decision to use remifentanil-PCA can only be made by a specifically trained doctor or a clinical midwife after informed consent of the patient. This is – at least partly- the result of the off-label use of remifentanil for labour analgesia leading to restrictions for its administration. These limiting factors are challenging to the current care in which shared decision making has become important. Previous studies showed that shared decision making contributes to a positive childbirth experience (19,20). The recent WHO recommendation 'Intrapartum care for a positive childbirth experience' states that "Effective communication and engagement among healthcare providers, health service managers, women and representatives of women's groups and women's rights movements is essential to ensure that care is responsive to women's needs and preferences in all contexts

and settings" (5). Although remifentanil-PCA is applied on a large scale at the request of labouring women, the off-label use of remifentanil formally results in restrictions for its application. As long as remifentanil is not registered for the indication labour analgesia healthcare providers have to find a balance between the restrictions related to its off-label status and the SOP and the importance of shared decision making.

In The Netherlands, currently there is no registration of the use of remifentanil-PCA and of SAEs attributed to the use of remifentanil-PCA. This is in contrast to other countries like Switzerland, Germany, United Kingdom, Singapore and Australia where hospitals are associated to the Swiss RemiPCA SAFE Network, although this association is not required. In these hospitals every application of remifentanil-PCA, including SAEs, is registered and contributes to the quality management of the use of remifentanil-PCA (21). In a Cochrane review, published in 2017, Weibel et al. recommended more research on both the maternal and neonatal side effects of remifentanil-PCA use as labour analgesia because of limited data on this subject (8). We found that the risk for an SAE attributed to the use of remifentanil-PCA is low corresponding with the risk found by Melber at al. (22). Although the occurrence of an SAE is very rare, these situations are unpredictable and life threatening and therefore claiming immediate awareness and treatment.

Surprisingly we observed in our study that several hospitals not fully comply with the SOP criteria for the maternal monitoring and/or for the dosage when administering remifentanil-PCA. Especially the observation that background infusion of remifentanil is still used simultaneously with bolus remifentanil-PCA in five hospitals is prominent. This observation is in accordance with a recent study of Hoenen et al. who investigated the compliance to the SOP in The Netherlands (23). The use of background infusion with remifentanil was associated with SAEs attributed to the use of remifentanil-PCA in previously published case reports (24–26). Moreover, in our study in five cases with apnea background infusion with remifentanil was used in addition to the bolus dosage.

The procedures for maternal monitoring during remifentanil-PCA use are still under discussion. Although Weiniger et al. found that measurements of oxygen saturation by pulse oximetry are inefficacious to detect apnea events, in clinical practice it is often the usual monitoring method. Weiniger et al. found that the most apnea events during remifentanil-PCA use are detected by continuous capnography of the respiratory rate or by the Integrated Pulmonary Index (IPI), which is a combination score of the respiratory and heart rate, oxygen saturation and end-tidal CO_2 (27).

However, the positive predictive value of continuous capnography and of the IPI is low resulting in many false alerts for apnea. False alerts may lead to alarm fatigue. Previous research - on other subjects than remifentanil-PCA - identified deaths as a consequence of alarm 'failure' (27). The ideal monitoring method should have a high specificity and a high sensitivity for detecting apnea. As long as such a method is not available one-to-one care during the whole period of the administration of remifentanil-PCA is relevant to detect respiratory

depression. In countries such as Switzerland and United Kingdom continuous one-to-one care during remifentanil-PCA use is required. In The Netherlands one-to-one care is – according to the SOP - required for at least one hour after the start of remifentanil-PCA and recommended during the whole period of administration of remifentanil-PCA. It is known from clinical practice and confirmed by Hoenen et al. that continuous one-to-one care during remifentanil-PCA use is not common in all Dutch hospitals (23). In our study, busy delivery units were mentioned as a barrier for the application of remifentanil-PCA. The adherence to strict maternal monitoring needing continuous one-to-one care to guarantee safety during remifentanil-PCA use and the feasibility for healthcare providers to accomplish this monitoring could be a challenge when remifentanil-PCA is used as labour analgesia.

Personalised medicine

In clinical practice it is a challenge to determine for which women remifentanil-PCA would suit best and for which women epidural analgesia. We developed and internally validated a treatment selection model for satisfaction with pain relief during labour (chapter 7). The final multivariable model contained treatment and the following variables: education level, previous vaginal delivery, antepartum fear of childbirth score, BMI, gestational age, ethnicity, risk category, dilatation, augmentation with oxytocin, as well as a treatment - ethnicity interaction and treatment - risk category interaction. The model identified 18.3% of the study group as women who would be satisfied with remifentanil-PCA. As an additional step we plan to repeat the analyses with the area under the curve after pain relief and with less variables to build a model that is easier to use in clinical practice. After external validation, the model may be applicable in clinical practice to select – at the moment of request for pain relief - women who would be satisfied with remifentanil-PCA during labour. The model could be helpful to identify women for whom remifentanil may be best suited. In practice an interplay between the model, the patient and the caregiver is needed to decide which method of pain relief is best suitable for the individual woman.

Recruiting of pregnant women in randomised controlled trials

Recruitment of patients in clinical trials, and of pregnant women in particular, is a complex process (chapter 8). This process is influenced on the one hand by the healthcare provider and the extent to which she/he is used to collaborating in clinical trials. On the other hand this process is influenced by personal factors of the candidate participant. The personal factors - influencing pregnant women in their decision whether to participate in a trial or not - we found are comparable with previous research (28–32). The most important motives for pregnant women to refuse participation in a clinical trial were a negative attitude towards the intervention and uncertainty about scientific research in general and particularly during pregnancy. These barriers are a long existing problem in the recruitment for clinical trials. So far, the ideal method to reach awareness and familiarity with scientific research among the public resulting

in an increase of participation of patients in clinical trials is unknown. In the United States the campaign 'Medical Heroes' started in 2003 and was initiated by a non-profit organisation and dedicated to educate the public and patients and to engage them in the clinical research process. They found for instance that those who participated in a clinical trial in the past are much more willing to participate again in general compared to those who never participated in a study (https://www.ciscrp.org/offer-item/medical-heroes)(33).

Methodological considerations

Area under the curve

In the RAVEL trials we expressed the primary outcome as an area under the curve (AUC). An advantage of the AUC is that it reflects a time weighted measure of the total satisfaction with pain relief which gives in our opinion a good indication of the pain experienced during the full duration of labour. Another advantage of the AUC is that the exact timing of the measurements is less relevant compared to single measurements of satisfaction with pain relief as used in previous studies. Besides, using an AUC a total image could be created even if only a few measurements were available. However, the translation of the AUC to individuals is challenging, as the duration of labour varies between women and the intensity over time also varies. How should we interpret an average AUC of – for example - 24? An AUC for pain intensity of 24 could indicate three hours with a pain score of eight, or eight hours with a pain score of three. So, the experiences of women could vary greatly, even if the same score has been observed. Therefore, we did not only look at the AUC to compare both methods of pain relief, but in addition we looked at the mean and highest satisfaction with pain relief during active labour and satisfaction with pain relief in retrospect, two hours and six weeks postpartum. These results support the conclusions based on the primary outcome.

Moment of randomisation

Due to the design of the RAVEL studies women were randomised during pregnancy and before the start of active labour as the Medical Ethics Committee considered randomisation during active labour to be unethical. The moment of randomisation might have been of influence on the outcome of the studies. For example, if a woman was randomised for the method of pain relief she did not prefer, the woman probably postponed her request for pain relief or even did not request for pain relief at all. As women knew already during their pregnancy for which method of pain relief they were randomised this could have influenced their adherence to the randomised method of pain relief at the moment of requesting pain relief. These possible effects of randomisation before active labour could have influenced the satisfaction with pain relief of these women. We assume that this influence counts for both the remifentanil-PCA and the epidural analgesia group.

Serious adverse events

In The Netherlands there is no registration of SAEs as a result of remifentanil-PCA use for labour analgesia. To investigate SAEs attributed to the use of remifentanil-PCA we were dependent on the reports of healthcare providers in our survey. Additionally we checked other sources where SAEs could have been reported. The number of reported cases could, despite our approach, be an underestimation of the real number of SAEs. Response bias might have occurred, possibly some respondents were not aware of an SAE or they could have been reluctant to report it. In addition, recall bias might have occurred as most of the reported cases date from several years ago and respondents mostly reported about the cases by remembrance and without the maternity care record at hand. To overcome these limitations we inquired at the Dutch Health Care Inspectorate and at The Dutch Pharmacovigilance Centre (Lareb) for additional reports of SAEs. In our opinion this resulted in a reproduction of SAEs as complete as possible.

Implications for practice

The experiences of women towards their satisfaction with remifentanil-PCA in combination with the risks of remifentanil-PCA should be taken into account when women are counselled about the experiences and risks of both remifentanil-PCA and epidural analgesia to make an informed choice.

In addition, a balance between shared decision making – about the most suitable method of pain relief- and the restrictions for the application of remifentanil-PCA according to the SOP should be considered in the procedure who decides to apply remifentanil-PCA. This should be taken into account in the ongoing revision of the Dutch guideline for 'Medical pain relief during labour'.

Once applied, strict maternal monitoring during remifentanil-PCA and the attendance of trained healthcare providers are required to prevent and to alert for an SAE. Although continuous one-to-one support is recommended for all labouring women anyway, as long as the ideal method for maternal monitoring is not available continuous one-to-one care for maternal monitoring is required to guarantee safety during remifentanil-PCA use. Complementary, registration of the use of remifentanil-PCA in the Dutch Perinatal Registry and registration of SAEs would make it possible to evaluate the administration of remifentanil-PCA and the safety of it. Systematic evaluation of SAEs is possible by a national registration by the Dutch Society of Obstetrics and Gynaecology or by a collaboration with the international RemiPCA SAFE Network. Simultaneously, the compliance to the SOP should be evaluated regularly and reported to The Dutch Health Care Inspectorate, who mandated the introduction of the SOP, in order to evaluate the safe administration of remifentanil-PCA. If maternity care providers consciously deviate from the SOP criteria patients should be informed about this prior to the use of remifentanil-PCA.

When looking at fear of childbirth postpartum epidural analgesia with continuous infusion does not seem to be preferred over remifentanil-PCA as method of pain relief. Fear of child-

birth antepartum is important to recognise because a childbirth experience is more affected by already existing fear of childbirth antepartum than by interventions or complications during labour (17,34). Midwives and obstetricians could discuss fear of childbirth with women during the prenatal visits. Once established, women can make an informed choice for treatment of their fear of childbirth in order to decrease the risk for obstetric interventions and for fear of childbirth reported postpartum (34,35). Besides, fear of childbirth is associated with higher perinatal costs. In this light is treatment of fear of childbirth also recommendable (36).

Furthermore, healthcare providers should be aware of the fact that patients are often not familiar with scientific research, specifically not during pregnancy. Extensive information about clinical trials in general - preferable before the patient is a candidate participant - could help to improve participation rates in clinical trials. We recommend the implementation of a national public campaign to improve familiarity with and knowledge about scientific research. Because of the general interest of scientific research a campaign and the evaluation of it could be a government investment, preferably already starting for people at high school.

Implications for research

The content of this thesis provides new insight in the use of remifentanil-PCA and helps to determine where to place remifentanil-PCA for labour analgesia. However, there are aspects still to be investigated to complete the thorough picture of remifentanil-PCA for labour analgesia. Preserving on this thesis the following research topics should be addressed:

1. Women's experience with the use of and how they value remifentanil-PCA. Knowledge of the experienced advantages and disadvantages of remifentanil-PCA by women could give additional information to select women who are most suitable for the application of remifentanil-PCA.
2. The optimal method for maternal monitoring during remifentanil-PCA. In chapter 6 we described that further investigation is necessary to find a balance between strict maternal monitoring to guarantee safety during remifentanil-PCA use and the feasibility for healthcare providers to accomplish this monitoring.
3. A systematic evaluation of the possible long-term effects on neonates could provide evidence about the long-term safety of remifentanil-PCA for labour analgesia. The long-term effects of the use of remifentanil-PCA on the health of the neonate were beyond the scope of this thesis.

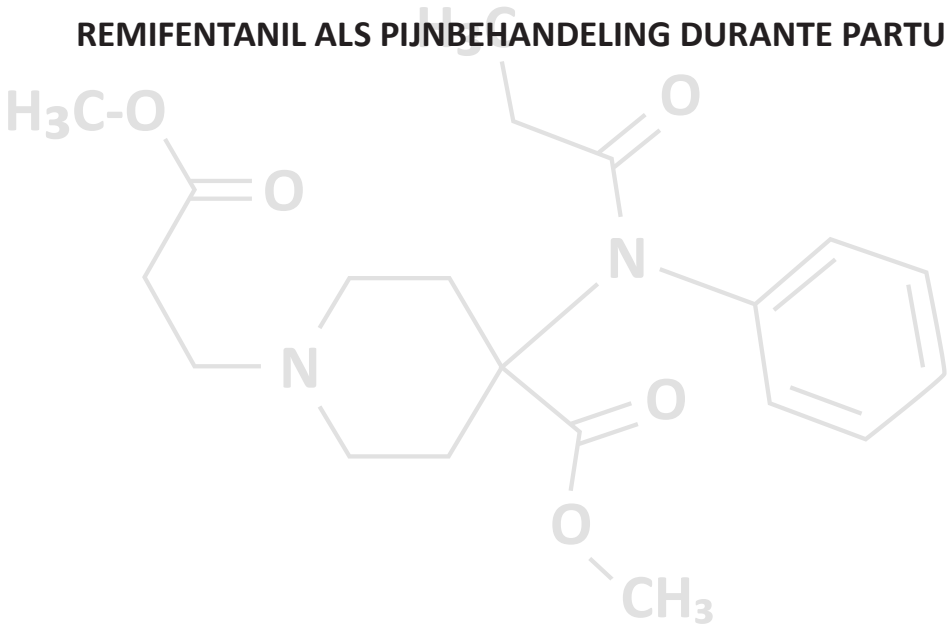
CONCLUSION

The studies of this thesis show that remifentanil-PCA for labour analgesia is used on a large scale in The Netherlands despite lower satisfaction with pain relief scores compared to epidural analgesia. Although we showed that the risk for an SAE is extremely low, the adherence to

strict maternal monitoring during remifentanil-PCA and the attendance of trained healthcare providers are essential to safely use remifentanil-PCA. To guarantee the safe administration of remifentanil-PCA, the compliance to the SOP and maternal monitoring methods during remifentanil-PCA have to be improved. If these conditions are met remifentanil-PCA is for certain women an appropriate method for labour analgesia.

Samenvatting & discussie

REMIFENTANIL ALS PIJNBEHANDELING DURANTE PARTU



SAMENVATTING

Dit proefschrift onderzoekt het gebruik van patiënt-gecontroleerde pijnbehandeling met remifentanil tijdens de baring (remifentanil patient controlled analgesia; remifentanil-PCA). Het doel van dit proefschrift is om bij te dragen aan de plaatsbepaling van remifentanil-PCA in het scala van pijnbehandelingen tijdens de baring. Wij onderzochten de tevredenheid van vrouwen met remifentanil-PCA ten opzichte van epidurale analgesie (ruggenprik). Ook keken wij naar de associatie tussen het gebruik van verschillende methoden van pijnbehandeling en angst voor de baring. Wij bestudeerden de veiligheid, beschikbaarheid en geschiktheid van remifentanil-PCA als pijnbehandeling tijdens de baring. Tot slot hebben wij onderzoek gedaan naar de uitdagingen rondom het rekruteren van zwangere vrouwen voor de deelname aan klinische studies vanuit het perspectief van zwangere vrouwen.

Hoofdstuk 1 presenteert een algemene inleiding over baringspijn, (niet) medicamenteuze methoden van pijnbehandeling en de huidige kennis over remifentanil-PCA als pijnbehandeling tijdens de baring. In dit hoofdstuk worden ook het doel en de onderzoeksvragen van dit proefschrift geïntroduceerd.

Hoofdstuk 2 & 3 rapporteren de resultaten van twee gerandomiseerde studies - RAVEL - waarin twee methoden voor pijnbehandeling tijdens de baring worden vergeleken bij vrouwen met een laag obstetrisch risico en bij vrouwen met een middelmatig tot hoog obstetrisch risico. Equivalentie voor remifentanil-PCA ten opzichte van epidurale analgesie kon niet worden aangetoond ten aanzien van tevredenheid met de pijnbehandeling, beschouwd over de totale duur van de baring. Deze uitkomst gold zowel voor vrouwen met een laag- als met een middelmatig tot hoog obstetrisch risico. Wij zagen dat vanaf de start van de pijnbehandeling de tevredenheid van vrouwen met epidurale analgesie hoger was dan bij vrouwen die remifentanil-PCA gebruikten. Aangezien remifentanil-PCA in het algemeen sneller beschikbaar is dan epidurale analgesie, kan remifentanil-PCA een alternatief zijn voor pijnbehandeling tijdens de baring.

In **Hoofdstuk 4** onderzochten wij de associatie tussen angst voor de baring en het gebruik van medicamenteuze pijnbehandeling bij vrouwen met een laag obstetrisch risico. Vrouwen die voorafgaand aan de baring angst hadden voor de baring vroegen vaker om pijnbehandeling tijdens de baring, maar deze associatie was niet statistisch significant. Vrouwen die medicamenteuze pijnbehandeling kregen, rapporteerden postpartum vaker dat ze tijdens de baring angst hadden ervaren dan vrouwen die geen medicamenteuze pijnbehandeling kregen. Als we kijken naar de score die vrouwen achteraf rapporteerden voor de angst die ze ervaren hadden tijdens de baring, lijkt epidurale analgesie met continue infusie niet te prefereren boven remifentanil-PCA als pijnbehandeling.

Hoofdstuk 5 beschrijft de resultaten van een vragenlijstonderzoek naar het huidige gebruik van remifentanil-PCA, onder gynaecologen in alle 81 Nederlandse ziekenhuizen met een verlosafdeling. Tussen de ziekenhuizen is veel variatie in het gebruik van remifentanil-PCA als pijnbehandeling tijdens de baring, variërend van 0 tot 56% van alle baringen. In de meeste

ziekenhuizen is remifentanil-PCA beschikbaar voor alle vrouwen, ondanks de restricties van de *Standard Operating Procedure* (SOP) opgesteld in opdracht van de Inspectie voor de Gezondheidszorg en Jeugd. De meest genoemde redenen voor de toepassing van remifentanil-PCA als pijnbehandeling tijdens de baring zijn 'de noodzaak van een alternatief voor epidurale analgesie' en 'op verzoek van zwangere vrouwen'.

Hoofdstuk 6 rapporteert de resultaten van een vragenlijstonderzoek onder gynaecologen, klinisch verloskundigen en anesthesisten naar het aantal *serious adverse events* (ernstige ongewenste voorvallen; SAEs) die zijn opgetreden als gevolg van het gebruik van remifentanil-PCA tijdens de baring. Wij vonden tien maternale casus van apneu; bradycardie en/of hartstilstand en twee neonatale casus van respiratoire depressie over een periode van meer dan tien jaar remifentanil-PCA gebruik in Nederland. Alle patiënten met een SAE herstelden volledig en zonder blijvende schade aan het eind van de behandeling. Hoewel de kans op een SAE zeer klein lijkt, zijn strikte maternale monitoring tijdens het gebruik van remifentanil-PCA en de aanwezigheid van getrainde zorgverleners voorwaardelijk om remifentanil-PCA veilig toe te passen.

Hoofdstuk 7 presenteert de resultaten van een secundaire analyse van de RAVEL studies. Wij onderzochten of wij konden identificeren welke barende vrouwen met een verzoek voor pijnbehandeling even tevreden zijn met remifentanil-PCA in vergelijking met epidurale analgesie. Wij ontwikkelden een multivariabel selectie model voor de tevredenheid met pijnbehandeling tijdens de baring. Het model werd intern gevalideerd en bevat naast de pijnbehandelingsmethode de variabelen: opleidingsniveau, zwangerschapsduur, eerdere vaginale baring, prenatale angst voor de baring, BMI, etniciteit, risico categorie, bijstimulatie met oxytocine, ontsluiting, interactie tussen behandelingsmethode-etniciteit en interactie tussen behandelingsmethode-risico categorie. Ons model identificeerde 18,3% van de studie groep als vrouwen die tevreden zouden zijn met remifentanil-PCA. Na externe validatie kan het model in de klinische praktijk worden gebruikt om – op het moment van een pijnbehandelingsverzoek- vrouwen te selecteren die tevreden zijn met remifentanil-PCA tijdens de baring.

Hoofdstuk 8 beschrijft de bevindingen van 21 semigestructureerde interviews met zwangere vrouwen die uitgenodigd waren om te participeren in een wetenschappelijke studie. Zij werden bevraagd over hun redenen om wel of niet deel te nemen aan een gerandomiseerde studie tijdens hun zwangerschap. Bijdragen aan wetenschappelijk onderzoek was voor de meeste deelnemers de belangrijkste motivatie om deel te nemen aan de studie, terwijl anderen gemotiveerd waren omdat de onderzochte interventie gunstig leek en niet beschikbaar was buiten studieverband. Een van de belangrijkste motieven voor zwangere vrouwen om niet deel te nemen aan de studie was een negatief gevoel ten aanzien van de interventie, omdat deze in de ogen van de zwangere mogelijk nadelig zou kunnen zijn voor de zwangere en/ of de foetus, of vanwege praktische redenen. Daarnaast observeerden we dat onzekerheid ten aanzien van wetenschappelijk onderzoek of ten aanzien van de interventie een belangrijk aspect was voor vrouwen.

ALGEMENE DISCUSSIE

Baringspijn

Baringspijn wordt in het algemeen beschouwd als zeer ernstige pijn. De ervaringen van vrouwen ten aanzien van baringspijn en de manier waarop er met baringspijn wordt omgegaan varieert aanzienlijk en wordt beïnvloed door interne- en externe factoren (1). Wereldwijd wordt er verschillend omgegaan met baringspijn, dit verandert in de loop van de tijd en is afhankelijk van onder andere de culturele achtergrond en de manier waarop de zorg is georganiseerd (2,3). Er is een variëteit aan (niet-) medicamenteuze methoden van pijnbehandeling, zowel om het omgaan met baringspijn te bevorderen als voor pijnbehandeling tijdens de baring. Continue begeleiding tijdens de baring is, onafhankelijk van de setting waarin het gegeven wordt, waarschijnlijk de belangrijkste interventie om een zo fysiologisch mogelijke baring na te streven. Het verbetert de tevredenheid over de baring en het is preventief voor (onnodige) medicalisering (4). Ondanks de aanbeveling voor continue begeleiding tijdens de baring is er – wereldwijd - een groeiende groep vrouwen die tijdens de baring medicamenteuze pijnbehandeling vraagt (5). Bij elke vrouw die verzoekt om pijnbehandeling is het de vraag welke methode van pijnbehandeling voor haar de meest geschikte methode is. Dit proefschrift verstrekt informatie over de plaats van remifentanil-PCA in het scala van pijnbehandelingen tijdens de baring. Deze informatie kan ook gebruikt worden voor de counseling van zwangere vrouwen over medicamenteuze pijnbehandeling.

Remifentanil-PCA

Ervaringen met remifentanil-PCA in vergelijking met epidurale analgesie

In beide RAVEL studies (hoofdstuk 2 en 3) konden wij geen equivalentie aantonen voor remifentanil-PCA. Wij vonden een vergelijkbare tevredenheid met pijnbehandeling met remifentanil-PCA en met epidurale analgesie, gemeten over de hele duur van de baring. Echter, gemeten vanaf de start van pijnbehandeling was de tevredenheid met de pijnbehandeling lager in de remifentanil-PCA groep. Volmanen et al. en Douma et al. vonden vergelijkbare tevredenheid tussen remifentanil-PCA en epidurale analgesie (6,7). Beide studies hadden beperkingen zoals tevredenheid als secundaire uitkomstmaat en een observatieperiode van tevredenheidsscores van slechts een uur. In beide RAVEL studies waren de pijnscores hoger in de remifentanil-PCA groep in vergelijking met epidurale analgesie groep, dit komt overeen met eerdere studies en een recente Cochrane review van Weibel et al. (1,8). Hoewel remifentanil-PCA als pijnbehandeling lagere tevredenheidsscores en hogere pijnscores geeft, heeft remifentanil-PCA voordelen ten opzichte van epidurale analgesie zoals de beschikbaarheid zonder de aanwezigheid van een anesthesist. Daarnaast kan remifentanil-PCA ook aan het eind van de ontsluitingsfase nog worden toegepast. Hoewel de meeste vrouwen waarschijnlijk de meest effectieve methode van pijnbehandeling prefereren, hebben sommige vrouwen mogelijk voorkeur voor een minder

invasieve methode met een lager niveau van pijnbehandeling, dit zagen wij ook in de RAVEL studies en het onderzoek naar praktijkvariatie van remifentanil-PCA (hoofdstuk 5). Voor deze vrouwen kan remifentanil-PCA worden overwogen.

In eerder onderzoek is gerapporteerd dat vrouwen die tijdens de baring epidurale analgesie gebruiken een verhoogd risico hebben op een vaginale kunstverlossing (9). In de RAVEL studies vonden wij echter geen verschil in het aantal vaginale kunstverlossingen bij vrouwen die gerandomiseerd waren voor remifentanil-PCA of voor epidurale analgesie. Dezelfde conclusie trekken Weibel et al. in een Cochrane review over remifentanil-PCA (8). Wij betwijfelen of deze bijwerking gerelateerd is aan de epidurale analgesie of dat het (deels) wordt veroorzaakt door *confounding by indication*. Een verzoek voor medicamenteuze pijnbehandeling kan geïndiceerd zijn door een niet vorderende baring of doordat een vrouw al in de latente fase zeer ernstige baringspijn ervaart. Mogelijk hebben vrouwen in deze situaties – ook zonder epidurale analgesie- een verhoogd risico op een vaginale kunstverlossing ten gevolge van abnormale progressie van de baring. Een recent gepubliceerde Cochrane review van Anim et al. over epidurale analgesie liet in een subgroep analyse van recente studies na 2005 geen toename zien van vaginale kunstverlossingen. Dit zou het resultaat kunnen zijn van het huidige beleid bij baringen met epidurale analgesie (10).

Remifentanil-PCA en angst voor de baring

In een secundaire analyse van de RAVEL studie richtten wij ons op vrouwen met een laag obstetrisch risico en angst voor de baring (hoofdstuk 4). Vrouwen met angst voor de baring vragen gewoonlijk vaker om pijnbehandeling dan vrouwen zonder angst voor de baring (11,12). Wij vergeleken onze resultaten met eerdere literatuur waarin angst voor de baring meestal werd onderzocht bij een heterogenere groep vrouwen, dat wil zeggen met zowel een laag- als een middelmatig tot hoog obstetrisch risico. Het voorkomen van antepartum angst voor de baring en postpartum gerapporteerde angst tijdens de baring bij vrouwen met een laag obstetrisch risico was vergelijkbaar met de literatuur (13–15). In overeenstemming met eerdere literatuur vonden wij dat vrouwen met antepartum angst voor de baring vaker om pijnbehandeling vroegen in vergelijking met vrouwen zonder angst voor de baring, hoewel ons resultaat niet statistisch significant was. De bevinding dat vrouwen die medicamenteuze pijnbehandeling gebruikten vaker postpartum angst tijdens de baring rapporteerden is in overeenstemming met eerdere studies (14,15). Postpartum gerapporteerde angst tijdens de baring kwam in onze studie vaker voor bij vrouwen die epidurale analgesie gebruikten vergeleken met vrouwen die geen pijnbehandeling kregen. Deze associatie was voor remifentanil-PCA niet statistisch significant. Het resultaat dat antepartum angst voor de baring sterk gerelateerd is aan postpartum gerapporteerde angst tijdens de baring is consistent met eerdere studies (15–18).

Praktijk variatie en serious adverse events in Nederland

Om een totaal beeld van remifentanil-PCA als pijnbehandeling tijdens de baring te creëren is kennis ten aanzien van de toepassing van remifentanil-PCA en het aantal *serious adverse events* (ernstige ongewenste voorvallen, SAEs) ten gevolge van het gebruik van remifentanil-PCA van belang (hoofdstuk 5 en 6). Wij lieten zien dat remifentanil-PCA, zowel in 2016 als in 2017, 21.000 keer per jaar in Nederland werd toegepast als pijnbehandeling tijdens de baring. Deze resultaten bevestigen de aanname van de Inspectie Gezondheidszorg en Jeugd (voorheen Inspectie voor de Gezondheidszorg) in 2013 dat remifentanil-PCA algemeen werd gebruikt als pijnbehandeling tijdens de baring en het impliceert dat een substantieel deel van de barende vrouwen kiest voor remifentanil-PCA als pijnbehandeling.

Eén van de belangrijkste motieven van gynaecologen om remifentanil-PCA beschikbaar te stellen was 'op verzoek van zwangere vrouwen'. Echter, de *Standard Operating Procedure* (SOP) voor het gebruik van remifentanil-PCA als pijnbehandeling tijdens de baring stelt dat er voor de patiënt nooit een vrije keuze kan zijn tussen remifentanil-PCA en epidurale analgesie. Volgens de SOP kan de beslissing om remifentanil-PCA toe te dienen alleen worden genomen door een specifiek daarvoor geschoolde arts of klinische verloskundige na *informed consent* van de patiënt. Dit is - tenminste gedeeltelijk- het gevolg van het off-label gebruik van remifentanil tijdens de baring wat tot restricties leidt voor de toepassing ervan. Deze beperkende factoren zijn een uitdaging in de huidige zorg waarin gezamenlijke besluitvorming belangrijk is. Eerdere studies lieten zien dat gezamenlijke besluitvorming bijdraagt aan een positieve bevallingservaring (19,20). De recente WHO aanbeveling *Intrapartum care for a positive childbirth experience* zegt hierover het volgende "Effectieve communicatie en betrokkenheid tussen zorgverleners, zorgmanagers, vrouwen, afgevaardigden van vrouwengroepen en vrouwenbewegingen voor de rechten van de vrouw, is essentieel om te garanderen dat de zorg beantwoord aan de behoefte van vrouwen en hun voorkeuren in alle contexten en plaatsen" (5). Zolang remifentanil niet is geregistreerd voor gebruik tijdens de baring zullen zorgverleners een balans moeten zoeken tussen de restricties gerelateerd aan de off-label status en aan de SOP en het belang van gezamenlijke besluitvorming.

Op dit moment wordt het gebruik van remifentanil-PCA en de incidentie van SAEs ten gevolge van remifentanil-PCA in Nederland niet geregistreerd. Dit is in tegenstelling tot andere landen zoals bijvoorbeeld Zwitserland, Duitsland, Engeland, Singapore en Australië waar ziekenhuizen vrijwillig samenwerken met het Zwitserse RemiPCA SAFE Network. In deze ziekenhuizen wordt elke toepassing van remifentanil-PCA tijdens de baring, en eventuele daaruit volgende SAEs, geregistreerd. Dit draagt bij aan het kwaliteitsmanagement van remifentanil-PCA (21). In een Cochrane review, gepubliceerd in 2017, deden Weibel et al. de aanbeveling om meer onderzoek te doen naar zowel maternale - als neonatale bijwerkingen ten gevolge van remifentanil-PCA (8). Wij vonden in onze studie dat het risico op een SAE ten gevolge van remifentanil-PCA gebruik extreem laag is, overeenkomstig de bevindingen van Melber et al.

(22). Hoewel SAEs zelden voorkomen, zijn deze situaties onvoorspelbaar en levensbedreigend en vereisen daarom onmiddellijke oplettendheid en behandeling.

Verrassend was de observatie in ons onderzoek dat meerdere ziekenhuizen niet voldoen aan alle SOP criteria voor maternale monitoring en/of dosering tijdens de toepassing van remifentanil-PCA. De bevinding dat, in vijf ziekenhuizen, remifentanil met achtergrondinfusie nog gelijktijdig met bolus dosering wordt gebruikt, is opvallend. Dit is overeenkomstig met een recente studie van Hoenen et al. die de naleving van de SOP in Nederland onderzocht (23). In eerder gepubliceerde case reports is het gebruik van achtergrondinfusie met remifentanil geassocieerd met SAEs ten gevolge van remifentanil-PCA (24–26). Daarnaast vonden wij in onze studie vijf casus met apneu waarbij naast de bolus dosering achtergrondinfusie met remifentanil werd gebruikt

De ideale maternale monitoring tijdens het gebruik van remifentanil-PCA staat nog ter discussie. Hoewel Weiniger et al. vonden dat saturatie metingen door middel van pulse oximetry niet doelmatig zijn voor het detecteren van apneu incidenten, is het in de klinische praktijk vaak de gangbare methode. Weiniger et al. vonden dat de meeste apneu's tijdens remifentanil-PCA worden gedetecteerd door middel van continue capnografie van de ademhalingsfrequentie of door middel van de *Integrated Pulmonary Index* (IPI), een combinatie score van de ademhalings- en hartfrequentie, zuurstofsaturatie en de eind-expiratoire CO_2 (27). Echter, de positief voorspellende waarde van continue capnografie en van de IPI is laag, wat resulteert in veel vals alarmmeldingen voor apneu. Veel vals alarmmeldingen kunnen leiden tot 'alarm moeheid'. Eerdere studies – met andere onderwerpen dan remifentanil- identificeerden incidenten met fatale afloop als een gevolg van alarm 'storing' (27). Idealiter wil men een technologie hebben met zowel een hoge specificiteit als een hoge sensitiviteit voor de detectie van apneu. Zolang deze technologie niet beschikbaar is, is een-op-een zorg tijdens de hele periode waarin remifentanil-PCA wordt toegepast relevant om respiratoire depressie tijdig te signaleren. In landen als Zwitserland en Engeland is continue een-op-een zorg tijdens remifentanil-PCA vereist. In Nederland is een-op-een zorg volgens de SOP gedurende het eerste uur na de start van remifentanil-PCA vereist en aanbevolen tijdens de hele periode waarin remifentanil-PCA wordt toegepast. Het is bekend vanuit de klinische praktijk en onderzocht door Hoenen et el. dat continue een-op-een zorg tijdens het gebruik van remifentanil-PCA echter niet in alle Nederlandse ziekenhuizen gangbaar is (23). Drukte op de verlosafdeling werd in onze studie als barrière genoemd voor de toepassing van remifentanil-PCA. Het voldoen aan strikte maternale monitoring met een-op-een zorg om de veiligheid tijdens de toepassing van remifentanil-PCA te garanderen en de haalbaarheid voor zorgverleners om deze monitoring uit te voeren kan een uitdaging zijn wanneer remifentanil-PCA wordt gebruikt als pijnbehandeling tijdens de baring.

Zorg op maat

In de klinische praktijk is het een uitdaging om te bepalen welke vrouwen tevreden zullen zijn met remifentanil-PCA en welke met epidurale analgesie. Wij ontwikkelden een model voor het

selecteren van de meest geschikte pijnbehandelingsmethode voor individuele vrouwen met als uitkomst de tevredenheid met de pijnbehandeling (hoofdstuk 7). Het multivariabele model bevat naast de pijnbehandelingsmethode de variabelen: opleidingsniveau, zwangerschapsduur, eerdere vaginale baring, prenatale angst voor de baring, BMI, etniciteit, risico categorie, bijstimulatie met oxytocine, ontsluiting, zowel interactie tussen behandelingsmethode en etniciteit als tussen behandelingsmethode en risico categorie. Het model identificeert 18,3% van de vrouwen voor wie remifentanil-PCA een acceptabel alternatief kan zijn voor epidurale analgesie. Wij zullen aangepaste analyses uitvoeren met minder variabelen, zodat het model makkelijker toepasbaar is in de klinische praktijk. Tevens zullen wij de *area under the curve* (AUC) voor de periode vanaf de pijnbehandeling gebruiken. Na externe validatie kan het model in de klinische praktijk worden gebruikt om – op het moment van het pijnbehandelingsverzoek- vrouwen te selecteren die tevreden zijn met remifentanil-PCA tijdens de baring. Het model kan bijdragen de juiste balans te vinden om remifentanil-PCA op de meest gunstige manier toe te passen ten opzichte van de meer invasieve epidurale analgesie, uitgaande van tevredenheid met de pijnbehandeling. In de klinische praktijk is een samenspel tussen het model, de zwangere en de zorgverlener nodig om te besluiten welke methode voor pijnbehandeling de meest geschikte is.

Rekruteren van zwangere vrouwen voor deelname aan gerandomiseerde studies

Het rekruteren van patiënten in klinische studies, en van zwangere vrouwen in het bijzonder, is een complex proces (hoofdstuk 8). Dit proces wordt aan de ene kant beïnvloed door de zorgverlener en aan de andere kant door persoonlijke factoren van de kandidaat deelnemer. De belangrijkste redenen voor zwangere vrouwen om niet deel te nemen aan een klinische studie waren negatieve associaties met de interventie en onzekerheid over wetenschappelijk onderzoek in het algemeen en specifiek tijdens de zwangerschap. Deze belemmeringen zijn een lang bestaand probleem bij het rekruteren voor klinische studies en zijn in overeenstemming met de literatuur (28–32). De ideale methode om bekendheid en bewustzijn met wetenschappelijk onderzoek te bereiken, resulterend in een toename van deelname aan klinische studies, is niet bekend. In de Verenigde Staten is in 2003 de campagne ‘Medische Helden’ gestart, geïnitieerd door een non-profit organisatie met als doel om het publiek en patiënten te scholen en aan te moedigen om deel te nemen aan klinische studies. Zij vonden bijvoorbeeld dat degene die eerder participeerde in een klinische studie meer bereid is om dat opnieuw te doen dan degene die niet eerder participeerde (https://www.ciscrp.org/offer-item/medical-heroes)(33).

Methodologische overwegingen

Area under the curve

In de RAVEL studies hebben wij de primaire uitkomst uitgedrukt als de *area under the curve* (AUC), de oppervlakte onder de lijn die over de tijd de tevredenheid met de pijnbehandeling

weergeeft. Een voordeel van de AUC is dat het een tijd gewogen weergave is van de totale tevredenheid met de pijnbehandeling. Naar ons idee is dat een goede indicatie van de ervaren tevredenheid met de pijnbehandeling tijdens de hele baring. Een ander voordeel is dat bij de AUC het exacte tijdstip van de metingen minder relevant is ten opzichte van losse metingen van tevredenheid met de pijnbehandeling, zoals in eerdere studies. Daarnaast kan de AUC ook worden berekend als slechts enkele metingen beschikbaar zijn. Echter, de vertaling van de AUC naar de individuele patiënt is uitdagend, zowel de tijdsduur van de baring als de intensiteit van de baringspijn varieert tussen vrouwen. Hoe interpreteer je bijvoorbeeld een AUC van 24? Een AUC van 24 kan bestaan uit drie uren met een pijnscore van acht of uit acht uren met een pijnscore van drie. Ook met dezelfde AUC kunnen de ervaringen van vrouwen heel verschillend zijn. Vandaar dat wij niet alleen de AUC berekenden om de beide pijnbehandelingen te vergelijken. Wij bekeken ook de gemiddelde- en de hoogste tevredenheid met de pijnbehandeling en de tevredenheid met de pijnbehandeling retrospectief gemeten, namelijk twee uur en zes weken postpartum. Deze resultaten ondersteunen onze conclusies gebaseerd op de primaire uitkomst.

Moment van randomisatie

Ten gevolge van het design van de RAVEL studies werden vrouwen gerandomiseerd tijdens de zwangerschap en voor de start van de baring omdat de medisch-ethische toetsingscommissie randomisatie tijdens de baring als onethisch beschouwde. Het moment van randomisatie kan invloed hebben gehad op de uitkomst van de studies. Bijvoorbeeld wanneer een vrouw gerandomiseerd was voor de methode van pijnbehandeling die niet haar voorkeur had, zou zij haar verzoek voor pijnbehandeling kunnen hebben uitgesteld of helemaal niet hebben gedaan. Tevens kan het design het trouw zijn van vrouwen aan de gerandomiseerde methode van pijnbehandeling hebben beïnvloed op het moment dat zij pijnbehandeling wensten, aangezien vrouwen al tijdens hun zwangerschap wisten voor welke methode zij waren gerandomiseerd. Deze effecten hebben mogelijk invloed gehad op de tevredenheid met de pijnbehandeling van deze vrouwen. We veronderstellen dat deze invloed geldt voor zowel de remifentanil-PCA als voor de epidurale analgesie groep.

Serious adverse events

Er is in Nederland geen registratie van SAEs als gevolg van het gebruik van remifentanil-PCA tijdens de baring. Om SAEs als gevolg van het gebruik van remifentanil-PCA te onderzoeken waren wij afhankelijk van de rapportage van zorgverleners in onze studie en wij deden navraag bij andere bronnen waar SAEs geregistreerd konden zijn. Het aantal gerapporteerde casus kan, ondanks onze brede benadering, een onderschatting zijn van het werkelijke aantal SAEs. *Response bias* kan zijn voorgekomen, mogelijk waren sommige respondenten niet op de hoogte van een SAE of waren zij terughoudend om een SAE te rapporteren. Daarnaast kan er in deze studie *recall bias* zijn opgetreden, omdat de meeste gerapporteerde casus dateren van een aantal jaar

geleden en de respondenten deels rapporteerden over de casus vanuit hun herinnering, zonder dat zij inzicht hadden in het dossier. Om deze beperkingen te ondervangen informeerden wij bij de Nederlandse Inspectie Gezondheidszorg en Jeugd en bij Lareb naar aanvullende rapportages over SAEs. Naar onze mening heeft dit geresulteerd in een zo compleet mogelijke reproductie van SAEs.

Implicaties voor de praktijk

Om zwangere vrouwen een geïnformeerde keuze te laten maken tussen remifentanil-PCA en epidurale analgesie moeten de risico's van en de ervaringen met remifentanil-PCA en epidurale analgesie in acht worden genomen bij de counseling over pijnbehandeling. Daarnaast zal de balans tussen gezamenlijke besluitvorming – ten aanzien van de voor deze vrouw meest geschikte methode van pijnbehandeling - en de restricties voor de toepassing van remifentanil-PCA volgens de SOP, beschouwd moeten worden in de procedure wie er besluit om remifentanil-PCA toe te passen. Dit kan tevens in overweging worden genomen bij de huidige herziening van de Nederlandse richtlijn 'Medicamenteuze pijnbehandeling durante partu'.

Strikte maternale monitoring tijdens het gebruik van remifentanil-PCA en de aanwezigheid van een getrainde zorgverlener zijn vereist ter preventie van een SAE en om een SAE tijdig te signaleren. Hoewel continue begeleiding tijdens de baring sowieso voor alle vrouwen is aan te bevelen, is continue een-op-een zorg vereist om een veilige toediening van remifentanil-PCA te garanderen zolang de ideale maternale monitoring nog niet beschikbaar is. Aanvullend, een reguliere registratie van het gebruik van remifentanil-PCA in de Nederlandse Perinatale Registratie en de registratie van SAEs zou het mogelijk maken om de toediening en de veiligheid van remifentanil-PCA te evalueren. Systematische evaluatie van SAEs kan plaatsvinden met een nationale registratie van SAEs door de Nederlandse Vereniging van Obstetrie & Gynaecologie of een samenwerking met het internationale RemiPCA SAFE Network. Tevens zou de naleving van de SOP regulier moeten worden geëvalueerd en gerapporteerd aan de Inspectie Gezondheidszorg en Jeugd, die de introductie van de SOP heeft opgedragen, teneinde de veilige toediening van remifentanil-PCA te garanderen. Als zorgverleners bewust afwijken van de SOP criteria moeten patiënten daarover worden geïnformeerd voorafgaand aan het gebruik van remifentanil-PCA.

Ten aanzien van ervaren angst tijdens de baring lijkt epidurale analgesie met continue infusie niet te prefereren boven remifentanil-PCA als pijnbehandeling tijdens de baring. Het is belangrijk om angst voor de baring te herkennen omdat de bevallingservaring meer wordt beïnvloed door reeds antepartum bestaande angst voor de baring dan door interventies of complicaties tijdens de baring (17,34). Verloskundigen en gynaecologen kunnen angst voor de baring tijdens de prenatale controles bespreken. Als angst voor de baring wordt herkend kunnen vrouwen een geïnformeerde keuze maken om hun angst te behandelen. Dit heeft als doel om de kans op zowel obstetrische interventies en complicaties als op postpartum gerapporteerde angst tijdens de baring te verkleinen (34,35). Daarnaast is angst voor de baring geassocieerd

met hogere perinatale kosten. In dit kader is behandeling van angst voor de baring ook aan te bevelen (36).

Zorgverleners zouden zich bewust moeten zijn van het feit dat patiënten vaak niet vertrouwd zijn met deelname aan wetenschappelijk onderzoek en specifiek niet tijdens de zwangerschap. Uitgebreide informatie over klinische studies in het algemeen - bij voorkeur voordat de patiënt een kandidaat deelnemer is - zou kunnen helpen om de deelname aan klinische studies te verbeteren. Wij bevelen de implementatie van een nationale publiekscampagne aan om de kennis van en bekendheid met wetenschappelijk onderzoek te vergroten. Vanwege het algemene belang van wetenschappelijk onderzoek zou deze campagne en de evaluatie ervan een investering van de overheid kunnen zijn, die bij voorkeur al start bij mensen in het voorgezet onderwijs.

Implicaties voor onderzoek

De inhoud van dit proefschrift geeft nieuwe inzichten in het gebruik van remifentanil-PCA en draagt bij aan de plaatsbepaling van remifentanil-PCA als pijnbehandeling tijdens de baring. Echter, er zijn aspecten die verder onderzoek behoeven om een zo compleet mogelijk beeld te krijgen van remifentanil-PCA. Op basis van dit proefschrift bevelen wij evaluatie aan van:

1. De ervaringen van vrouwen met en hun waardeoordeel over remifentanil-PCA. Kennis van de door de vrouw ervaren voor- en nadelen van remifentanil-PCA geeft aanvullende informatie welke vrouwen geschikt zijn om remifentanil-PCA te gebruiken.
2. De optimale maternale monitoring tijdens het gebruik van remifentanil-PCA. In hoofdstuk 6 beschreven wij dat aanvullend onderzoek nodig is om een balans te vinden tussen strikte maternale monitoring om de veiligheid tijdens de toepassing van remifentanil-PCA te garanderen en de haalbaarheid voor zorgverleners om deze monitoring uit te voeren.
3. Een systematische evaluatie van de mogelijke lange termijn effecten van remifentanil op de neonaat kan wetenschappelijk bewijs geven over de lange termijn veiligheid van remifentanil-PCA tijdens de baring. De lange termijn effecten van het gebruik van remifentanil-PCA op de gezondheid van de neonaat vielen buiten de scope van dit proefschrift.

CONCLUSIE

De studies van dit proefschrift laten zien dat remifentanil-PCA in Nederland op grote schaal wordt toegepast als pijnbehandeling tijdens de baring ondanks een lagere tevredenheid in vergelijking met epidurale analgesie. Hoewel wij hebben laten zien dat het risico op een SAE extreem laag is, zijn strikte maternale monitoring en de aanwezigheid van getrainde zorgverleners essentieel om remifentanil-PCA veilig te gebruiken. Om een veilige toediening van remifentanil-PCA te garanderen moeten de naleving van de SOP en de maternale monitoring worden verbetert. Als aan deze voorwaarden wordt voldaan is remifentanil-PCA voor een groep vrouwen een geschikte methode van pijnbehandeling tijdens de baring.

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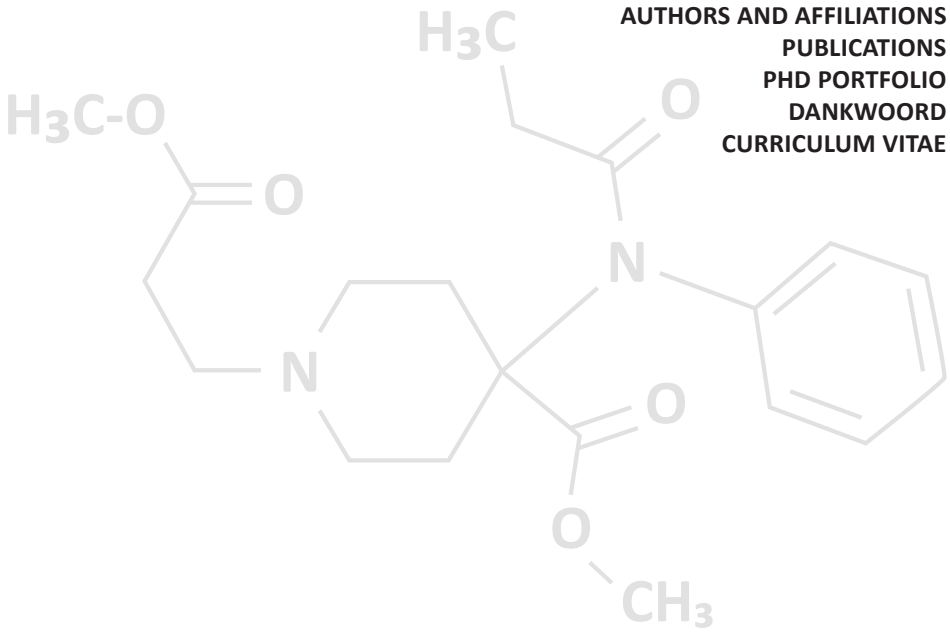
CHAPTER 10

Addendum



ABBREVIATIONS

aOR	Adjusted Odds ratio
ASA	American Society of Anesthesiologists
AIC	Akaike Information Criterion
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CSE	Combined spinal – epidural
EA	Epidural analgesia
HADS	Hospital Anxiety Depression Scale
ICU	Intensive Care Unit
IQR	Interquartile range
MICE	Multivariate Imputations by Chained Equations
$MgSO_4$	Magnesium sulfate
N_2O	Nitrous oxide
OR	Odds ratio
PRN	Dutch Perinatal Registry
RAVEL study	Remifentanil patient controlled Analgesia Versus Epidural analgesia Study
RPCA	Remifentanil patient controlled analgesia
SAE(s)	Serious adverse event(s)
SD	Standard deviation
SE	Standard error
SOP	Standard Operating Procedure
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual analogue scale
W-DEQ	Wijma Delivery Expectancy/Experience Questionnaire
W-DEQ A	Wijma Delivery Expectancy/Experience Questionnaire antepartum version
W-DEQ B	Wijma Delivery Expectancy/Experience Questionnaire postpartum version

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PUBLICATIONS

Oude Rengerink K, Opmeer BC, **Logtenberg SL**, Hooft L, Bloemenkamp KW, Haak MC, Oudijk MA, Spaanderman ME, Duvekot JJ, Willekes C, van Pampus MG, Porath MM, van Eyck J, Sikkema MJ, Mol BW. IMproving PArticipation of patients in Clinical Trials--rationale and design of IMPACT. *BMC Med Res Methodol. 2010 Sep 27;10:85. doi: 10.1186/1471-2288-10-85.*

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Freeman LM, Bloemenkamp KW, Franssen MT, Papatsonis DN, Hajenius PJ, Hollmann MW, Woiski MD, Porath M, van den Berg HJ, van Beek E, Borchert OW, Schuitemaker N, Sikkema JM, Kuipers AH, **Logtenberg SL**, van der Salm PC, Oude Rengerink K, Lopriore E, van den Akker-van Marle ME, le Cessie S, van Lith JM, Struys MM, Mol BW, Dahan A, Middeldorp JM. Patient controlled analgesia with remifentanil versus epidural analgesia in labour: randomised multicentre equivalence trial. *BMJ. 2015 Feb 23;350:h846. doi: 10.1136/bmj.h846.*

Sabine L.M. Logtenberg, Katrien Oude Rengerink, Corine J. Verhoeven, Liv M. Freeman,Eline S.A. van den Akker, Marc B. Godfried, Erik van Beek, Odette W.H.M. Borchert, Nico Schuitemaker, Liesbeth E.C.S.M. van Woerkens, Ilse Hostijn, Johanna M. Middeldorp, Joris A. van der Post, Ben Willem J. Mol. Labour pain with remifentanil patient controlled analgesia versus epidural analgesia; a randomised equivalence trial. *BJOG. 2016, June 27. doi: 10.1111/1471-0528.14181*.

Sabine Logtenberg, Leonoor Vink, Corine Verhoeven, Katrien Oude Rengerink, Ingrid Beenakkers, Liv Freeman, Annemieke Middeldorp, Marc Godfried, Francois Schellevis, Ben Willem Mol. Practice variation of remifentanil-PCA in the Netherlands. *Ned Tijdschr Geneeskd. 2018;162(D2816).*

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Sabine L.M. Logtenberg, Ben Willem J. Mol, Corine J. Verhoeven. Epidural analgesia is no rescue-treatment. *Under review: The Lancet*

PHD PORTFOLIO

Courses

2015	Scientific writing in English
2015	Communication with patients
2016	Practical Biostatistics
2017	Endnote
2018	Searching for CAT
2018	Searching for Evidence
2018	Project Management

Workshop, seminar, master class

2018	APH-QoC workshop, Amsterdam
2018	Annual Care Meeting, 's-Hertogenbosch
2018	Master Class: 'Praktijkvariatie', Utrecht

Oral presentations

2011	Annual meeting of Society for Maternal-Fetal Medicine, San Francisco, USA. "Partcipating in Clinical Trials?"
2017	APH annual meeting, Amsterdam. "Which labouring women needing pain relief benefit from controlled analgesia with remifentanil and which women benefit from epidural analgesia?"
2018	Normal Labor and Birth, Michigan, USA. "Pharmacological pain relief and fear of childbirth in low risk women; secondary analysis of the RAVEL study"

Poster presentations

2012	Society for Clinical Trials (SCT), Miami. "Pregnant women's views about participation in trials- a qualitative study"
2014	ESRA Congress, Sevilla. "Remifentanil-PCA versus epidural analgesia during labour"
2015	Intrapartum Congress, Porto. "Remifentanil-PCA versus epidural analgesia during labour"
2018	BIRTH Congress, Venice, Italy. "Pharmacological pain relief and fear of childbirth in low risk women; secondary analysis of the RAVEL study"
2018	BIRTH Congress, Venice, Italy. "Serious adverse events attributed to remifentanil patient controlled analgesia during labour in The Netherlands"

Other relevant activities

2012	Consortium Training Days, Veldhoven
2012	Monitoren van mens gebonden onderzoek en QA/QC bevindingen, Veldhoven
2013	Data Safety Monitoring, Utrecht
2017	Round the Table meeting Remi Safe Network, Obstetric Anaesthesia Congress, Brussels, Belgium
2017	APH annual meeting, Amsterdam
2018	Symposium De eerste 1000 dagen van het leven, Amsterdam
2018	APH annual meeting, Amsterdam
2016-2018	Midwifery Science, promovendidagen, Zwolle

International conferences

2011	Annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, USA
2013	XI World Congress of Perinatal Medicine, Moscow, Russia
2015	Intrapartum Congress, Porto, Portugal
2018	Normal Labor and Birth Congress, Michigan, USA
2018	BIRTH Congress, Venice, Italy

Tutoring, mentoring

2017-2018	Student mentoring/supervising scientific research project Leonoor Vink

Grant

2017	APH Personalized Medicine 2017: Personalizing analgesia during labour: which labouring women needing pain relief benefit from controlled analgesia with remifentanil and which women benefit from epidural analgesia?

DANKWOORD

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En dan het promotieteam: mijn promotoren Prof. dr. B.W. Mol, Prof. dr. F.G. Schellevis, mijn co-promotores dr. C.J.M. Verhoeven en dr. K. Oude Rengerink.

Beste Ben Willem, de eerlijkheid gebiedt te zeggen dat mijn promotie jouw idee was. Jij gaf mij de kans om zelf onderzoek te gaan doen en regelmatig vroeg je terloops hoe het met 'het P-woord' ging. Die toespelingen op een promotietraject nam ik lange tijd niet serieus. Maar je hebt dat net zo lang volgehouden totdat een promotie ook voor mij een serieuze optie werd. Je hebt mij veel geleerd, gestimuleerd, het vertrouwen gegeven en, ook vanuit Australië, geduldig begeleid. Tijdens je bezoeken aan Nederland was er altijd tijd voor overleg. Frequent sprak ik je bij 'Sheraton The Gate' op Schiphol of in een café in het centrum van Amsterdam. Deze gesprekken begonnen standaard met jouw mening over de prestaties van Ajax en aansluitend de vraag wat mijn zoon Gijs van deze prestaties vond. Als we het onderzoek bespraken was je kritisch, humoristisch, direct, opbouwend en constructief. Dat heb ik zeer gewaardeerd. Vaak sloot je het overleg af met de, in jouw ogen relativerende, opmerking: "Je moet het alleen nog even opschrijven". Ik heb veel respect voor je ongeëvenaarde gedrevenheid en inzet om de verloskundige zorg te verbeteren. Het ga je goed in Melbourne.

Beste François, door mijn switch van baan naar de Verloskunde Academie werd jij halverwege het promotietraject mijn tweede promotor. Vanaf onze eerste kennismaking was ik blij door jou te worden begeleid. Je was rustig, duidelijk, positief, kritisch en je helicopterview was verhelderend als ik mij afvroeg hoe we bepaalde problemen zouden aanpakken. Jouw constructieve en snelle feedback op concepten maakten het manuscript altijd beter. Wat 'n geluk dat ik als een van de laatsten in je carrière nog mocht 'profiteren' van jou als promotor.

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Lieve Juut, het is ongelooflijk te bedenken dat wij in 1990 samen begonnen aan de opleiding en nu hier staan. Vanaf dag één waren we vriendinnen, roeiden bij Nereus, reisden maanden door Chili en Bolivia en bleven bevriend ondanks de afstand Amsterdam-Maastricht. Dat we nu bijna tegelijkertijd promoveren bij dezelfde promotor hier in Amsterdam is de ultieme bekroning van onze vriendschap.

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CURRICULUM VITAE

Sabine Logtenberg werd op 16 juni 1970 geboren in Borne als tweede dochter in een gezin van vier kinderen. Zij behaalde in 1989 haar VWO-diploma aan het Thomas a Kempis College in Zwolle. Daarna volgde zij de opleiding tot verloskundige aan de Vroedvrouwenschool in Amsterdam (thans Academie Verloskunde Amsterdam Groningen), waar zij in 1993 cum laude afstudeerde. Zij werkte enkele jaren als waarnemend verloskundige in Amsterdam, Harderwijk en Leeuwarden waarna zij in 1995 associeerde in de 'Verloskundemaatschap Astrid Limburg' in Amsterdam.

In 2002 stapte zij over van de eerste naar de tweedelijnszorg en ging werken als klinisch verloskundige in het Onze Lieve Vrouwe Gasthuis in Amsterdam (thans OLVG-Oost). Tevens coordineerde zij hier gedurende zeven jaar de obstetrische consortiumstudies. In 2011 voltooide zij de opleiding tot *master physician assistant* (klinisch verloskundige) aan de Hogeschool Rotterdam. Eind 2012 begon zij aan het onderzoek voor dit proefschrift. Sinds 2015 is zij werkzaam als docent aan de Academie Verloskunde Amsterdam Groningen, waarvoor zij in 2016 haar 'basis didactische bekwaamheid' haalde. Tot voor kort was zij praktiserend klinisch verloskundige in het OLVG; werk dat zij combineerde met haar onderwijstaken en promotietraject.

Sabine is getrouwd met Iskander Breebaart. Samen hebben zij twee zonen: Mart (2000) en Gijs (2002), beiden kwamen ter wereld in het OLVG. Bij haar eerste baring kreeg ze spinale anesthesie. De tweede baring was zonder pijnbehandeling.