Remifentanil for labour pain : safety and efficacy

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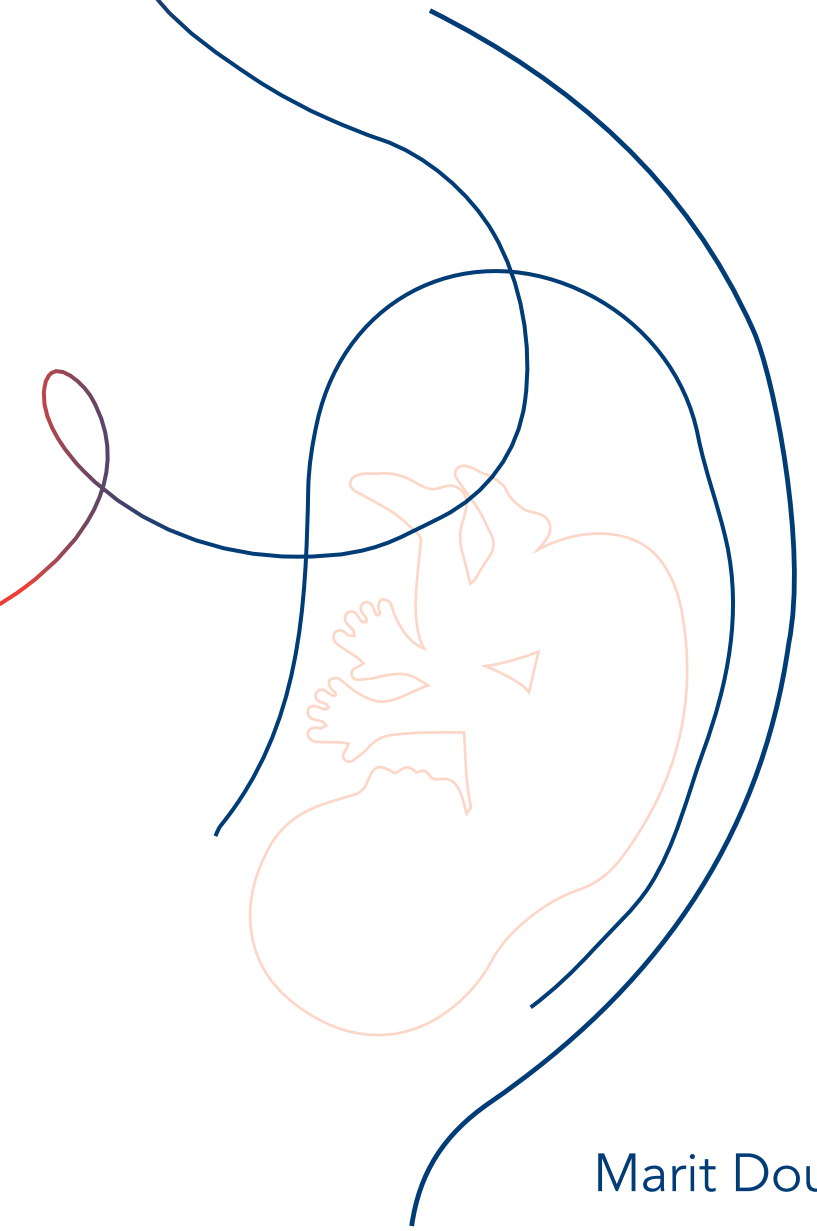

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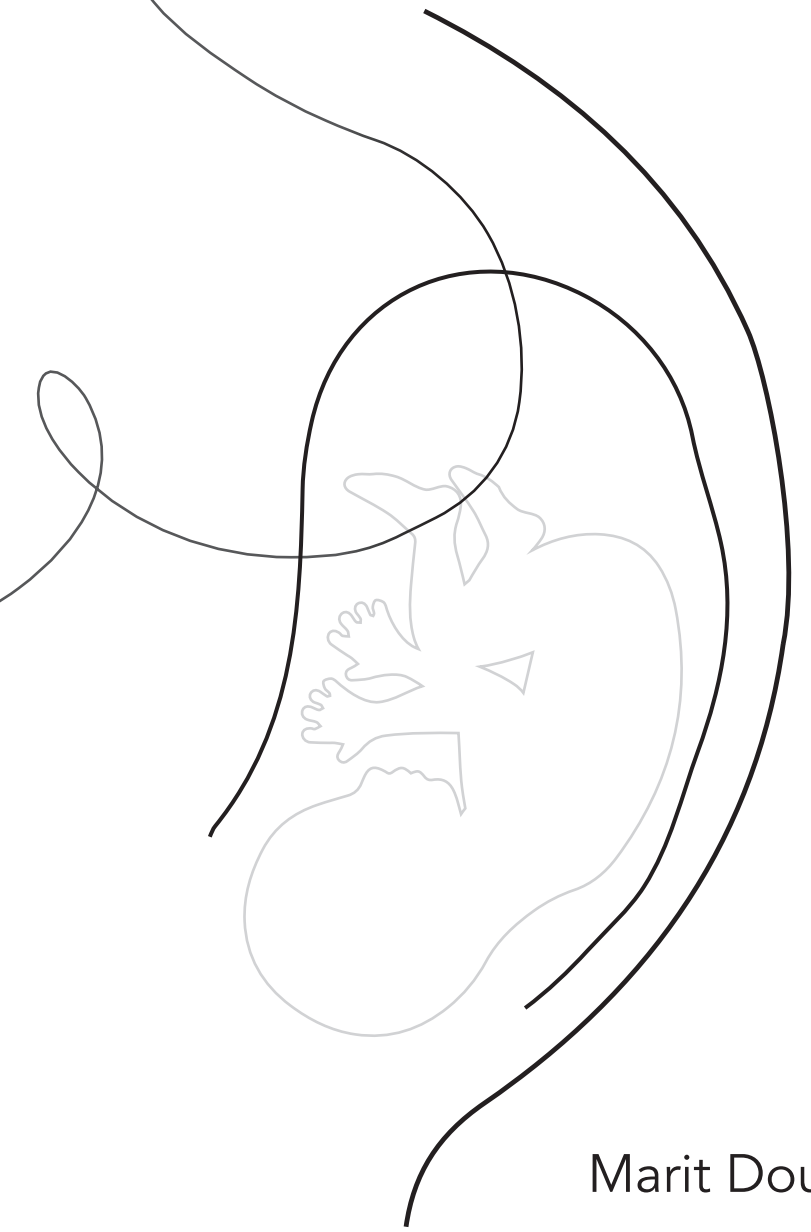

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Remifentanil for labour pain: safety and efficacy

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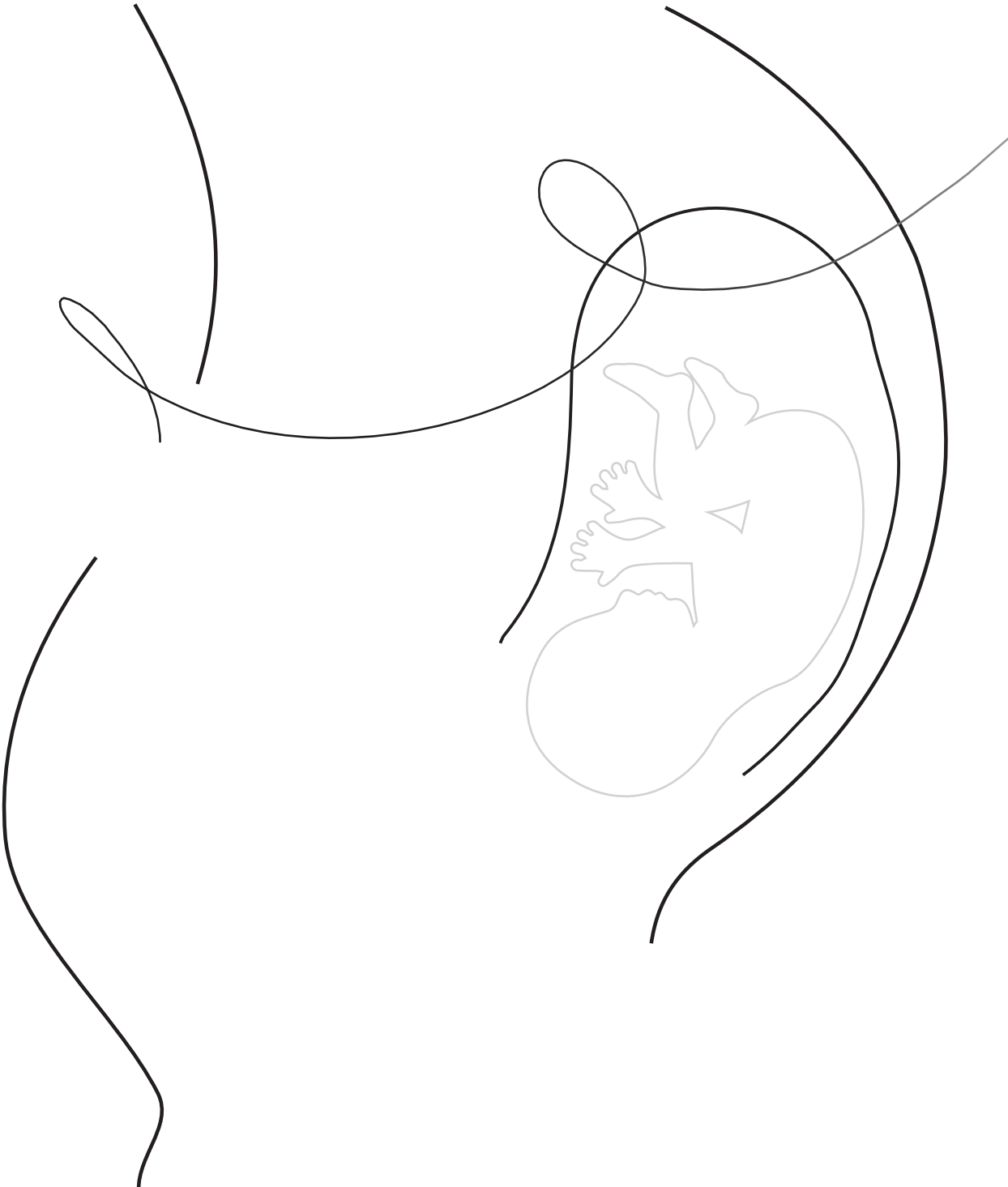

Contents

Chapter 1

General introduction

Most women describe the pain of childbirth as one of the most intense forms of pain that can be experienced during their life, although the intensity of pain parturients experience during labour can vary.[1, 2]
Pain during the first stage of labour is mainly visceral in nature and arises from the uterus and cervix. It is the result of dilatation of the cervix and distension of the lower uterine segment during contractions.[3] The pain is transmitted via spinal nerves T10 through L1. During the second stage of labour, when the cervix is fully dilated, pain occurs from stretching and tearing of tissues of vagina, perineum and pelvic floor. This somatic pain is transmitted via the pudendal nerve, entering the spinal cord via nerve routs S2-S4.[4]

Throughout history, treating labour pain has been a controversial topic. The oldest form of pain relief and still in use today is opium. Opium was discovered around 3400 BC. In the 19th century, separation of active components of opium became possible and its principle ingredient morphine could be isolated. In 1847, the Scottish obstetrician James Young Simpson was the first person administering chloroform and ether as labour analgesic. Although many considered labour analgesia unnatural, against religious beliefs and probably harmful, it rapidly became popular. Even Queen Victoria used chloroform during the birth of Prince Leopold (1853). In the early 1900s nitrous oxide, originally discovered in 1799 by Davis, an English chemist, was being used as labour analgesic. In the 1940s neuraxial analgesia during labour was introduced by John Bonica, an American anesthesiologist. His wife was one of the first women to receive an epidural for the birth of their child.[5] In 1947, John Bonica, at that time head of the department of Anesthesiology at Tacoma Hospital, organised one of the first round-the-clock labour analgesia services. From 1960 on, when Bonica was chairman of the department of Anesthesiology of University of Washington, caudal analgesia became the primary technique for treating labour pain.[6]

Today, there are several options to reduce labour pain, including both non-pharmacological and pharmacological methods. Non-pharmacological methods include (self-) hypnosis, sterile water injections, water immersion (pool or bath), aromatherapy, relaxation techniques (yoga/mediation), acupuncture/acupressure and transcutaneous electrical nerve stimulation (TENS). The aim of non-pharmacological options is primarily to help cope with the pain, whereas pharmacological methods aim to relieve the pain of labour.[4] Pharmacological interventions include inhaled analgesia, opioids, local anesthetic nerve blocks and neuraxial analgesia.

Of inhaled analgesia, nitrous oxide (in 50% oxygen) is used in obstetric analgesic practice. Advantages of the technique are easy administration, absence of effect on uterine contractions, minimal effect on maternal hemodynamic parameters and a rapid onset and offset of action. Nitrous oxide is widely administered in the United Kingdom and Scandinavia. The use of nitrous oxide in the Netherlands has declined considerably since the introduction of strict occupational exposure limits. These limits were introduced because epidemiologic studies showed increased reproductive risks (e.g. miscarriage, congenital anomalies and reduced rates of fertility) for health professionals who were frequently exposed to nitrous oxide.[7] With the advent of new scavenging systems, the use of nitrous oxide has regained some popularity.

Opioids are relatively inexpensive and easy to administer. Parental and intramuscular administered opioids during labour include morphine, nalbuphine and fentanyl. The most commonly used systemic opioid is pethidine, although its efficacy is being challenged for some time now.[8-10] In general, up to two-thirds of women who receive opioids during labour report only poor or moderate pain relief. Moreover, opioid drugs are associated with maternal nausea, sedation and drowsiness.[11] For the neonate, respiratory depression can occur.

Of the local anesthetic nerve blocks, pudendal and paracervical nerve blocks are most commonly used in obstetrics. A pudendal block can be performed during the second stage of labour by injection of a local anesthetic around the trunk of the pudendal nerve.[4]

Epidural analgesia is a central nerve blockade technique, which involves the injection of a local anesthetic, with or without an opioid, into the lower region of the spine close to the nerves that transmit painful stimuli from the contracting uterus and birth canal.[12] It is proven to provide effective pain relief during labour. Possible maternal side effects include hypotension, pruritus, an increase in temperature and urinary retention. A Cochrane review, published in 2011, concluded epidural analgesia was associated with increased risk of instrumental delivery.[12] Among the pharmacological methods of pain relief, epidural analgesia is considered to be the most effective form or 'gold standard'. Nevertheless, even in the developed world, epidural analgesia is not always available to all parturients. This can have several reasons. There can be an absolute or relative contra-indication to the use of central neuraxial analgesia or it is possible that labour progresses too rapidly. There can be logistic problems, as an anesthesiologist is required to perform the procedure. Therefore, there is need for other effective obstetric analgesics to provide an alternative.

Remifentanil is a synthetic opioid with direct agonist action specifically at the μ-opioid receptor. It has been developed for usage during general anesthesia under conditions of strict monitoring and is further used for deep sedation, again under conditions of strict monitoring. The opioid became FDA approved in 1996 and the first case report on use of remifentanil as labour analgesic appeared in 1999.[13] Over the last 15 years remifentanil patient-controlled analgesia (PCA) has become an increasingly popular labour analgesic, however, the opioid is not officially registered for obstetric analgesic use. Remifentanil has an unique pharmacokinetic profile with a short terminal half-life due to hydrolysis by non-specific blood and tissue esterases and consequently a metabolism independent of renal and/or kidney function. It has a rapid onset of action and short latency to its peak effect, which makes it very suitable for PCA.[14] Remifentanil crosses the placenta, but is rapidly metabolized and/or redistributed by the fetus.[15] Adverse effects resemble those of other potent opioid analgesics and include respiratory depression with oxygen desaturation and sedation.[16 17]

The aim of this thesis was to evaluate the efficacy and safety of remifentanil in its treatment of labour pain.

In chapter 2 a randomised controlled trial is performed comparing the analgesic efficacy of remifentanil to pethidine and fentanyl, in a patient controlled setting.

In chapter 3 remifentanil PCA is compared to epidural analgesia with respect to analgesic efficacy in a randomised controlled study.

Chapter 4 describes a randomised controlled trial comparing side effects of remifentanil PCA and epidural analgesia.

In Chapter 5 pharmacokinetic pharmacodynamic modelling and simulation studies are presented, using data from a previous study on the effect of iv remifentanil on ventilation in healthy volunteers. We aimed to better understand the effect of remifentanil PCA during labour on ventilation, rather than on surrogate markers of ventilation such as oxygen saturation.

In Chapter 6 a systematic review is performed on data from trials on side effects of remifentanil and other labour analgesics.

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Chapter
1

Chapter 2

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

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INTRODUCTION

Epidural analgesia is considered to be the most effective method of pain relief during labour. However, there are situations in which epidural analgesia is contra-indicated, for example patients with coagulation or platelet disorders or refusal of epidural analgesia.
At this moment, the most commonly used alternative for epidural analgesia is (intramuscular) meperidine, although its efficacy is widely challenged.[1-3]
For these reasons there is great need for new analgesic methods during labour.

Remifentanil, the hydrochloride salt of 3-[4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino] -1-piperidine] propanoic acid methyl ester, is a synthetic opioid (anilidopiperidine) with direct agonist action specifically on μ-opioid receptors. Its rapid hydrolysis by non-specific blood and tissue esterases to an inactive metabolite, results in a very short duration of action. The pharmacodynamic profile of remifentanil is characterized by a rapid onset of action and short latency to its peak effect. The context-sensitive half-life is ~3 to 4 min and the elimination half-time ranges from 10 to 20 minutes. Most of an intravenous dose is excreted in the urine as the carboxylic acid metabolite. The metabolism of remifentanil is independent of renal and hepatic function and there is no accumulation during repeat bolus injection.[4 5]
Placental transfer of remifentanil does occur but in the neonate it appears to be rapidly metabolized, redistributed, or both.[6] The rapid onset and offset of remifentanil are suitable characteristics for patient controlled analgesia (PCA).

Another possible opioid during labour is fentanyl. Fentanyl PCA during labour has been studied before.[7-9] One study compared intravenous fentanyl with intravenous meperidine during labour and found that fentanyl was preferable to meperidine because there appeared to be less maternal side effects and fewer requirements for naloxone.[10]
There are no studies comparing these three opioids in a patient-controlled method. A recent Belgian survey investigating the use of analgesic alternatives to epidural analgesia showed that remifentanil was the first choice when using patient-controlled intravenous analgesia, but other opioids including sufentanil and fentanyl were also used.[11]
The main objective of this prospective, randomised, double-blind study was to compare the analgesic efficacy of remifentanil with meperidine and fentanyl in a patient-controlled intravenous analgesia setting.

METHODS

The study protocol was approved by the local Research Ethics Committee. After obtaining written informed consent in the antenatal clinic or before the onset of active labour, 180 women requesting analgesia other than epidural analgesia were studied. All women were healthy (ASA physical status I or II) term parturients in an active stage of labour, with singleton cephalic presentation, without prior administration of opioid analgesics. Exclusion criteria included obesity (BMI ≥ 40 kg/ m^2), opioid allergy, substance abuse history and high risk patients (pre-eclampsia, severe asthma, insulin dependent diabetes mellitus, hepatic insufficiency or renal failure).

Randomisation was established by using a computer-generated random sequence in numbered envelopes. Women were randomly allocated to one of three groups, each group containing sixty parturients. Study medication was prepared and blinded by the hospital pharmacy. There were three pre-programmed PCA devices (Braun Perfusor fm PCA) available, each set to deliver the corresponding dose and with the appropriate lock-out interval. Observants and medical personnel attending to the parturient were unaware of the drug assignment.

Women allocated to the remifentanil group (group R) received a 40 µg remifentanil loading dose and remifentanil 40 µg per bolus with a lockout of 2 minutes and a maximum dose limit of 1200 µg per hour. The specific dose regimen was based on previous studies.[12 13] Women randomised to receive meperidine (group P) received a 49,5 mg meperidine loading dose and 5 mg boluses with a lockout of 10 minutes and a maximum overall dose limit of 200 mg. Women in the fentanyl group (group F) received a 50 µg loading dose and boluses of 20 µg with a lockout of 5 minutes and a maximum dose limit of 240 µg per hour.[9] All women received similar instructions how to use the PCA device: All parturients were instructed to press the bolus button whenever they needed pain relief. They were told to press the button as often as they felt necessary and it was explained that each pump was programmed to monitor the total dose administered and that safety limits were set to avoid an overdose. It was explained that this implied the possibility that not every request would be rewarded. All women were free to cross over to epidural analgesia at any time. The PCA device was discontinued at full cervical dilatation.

With the exception of baseline data, all observations and measurements were made by blinded observers. Observants entered the delivery room only after the PCA device had been connected and the loading dose had been administered. This way the observants were unable to notice time differences in the administration of the loading dose, which might have jeopardized blinding. Observants had no knowledge of the

differences in programming of the PCA devices. Non-invasive measurements were made before starting the study protocol and at regular intervals thereafter, including maternal arterial pressure, heart rate, ventilatory frequency, and pulse oximetry. Measurements were recorded every 30 minutes. Hypotension (systolic arterial pressure <90 mmHg or > 25% below baseline) was treated with intravenous fluids and ephedrine 5 mg i.v.. When oxygen saturation decreased below 95%, oxygen 6 litre/min was administered by facemask.

Pain scores were assessed using a visual analogue scale (VAS) ranging from 0-10 cm. Women were asked to mark the level of pain experienced during contractions every hour, starting with a baseline VAS score before institution of analgesia. In addition, an observer sedation score (1= awake, 2=sleepy, 3=eyes closed, but rousable by vocal stimulus, 4= eyes closed, but rousable by physical stimulus, 5= unrousable) was recorded hourly. Two hours after delivery the parturients were asked to score their overall satisfaction on a ten-point scale (1-10).

Fetal heart rate and uterine activity were measured continuously by external monitoring. When data were difficult to interpret or in case of complications (such as meconium stained amniotic fluid, failure to progress in labour), invasive monitoring by means of scalp electrode and intra-uterine pressure recording was instituted. Fetal heart rate patterns were scored as reactive or non-reactive at regular intervals by an obstetrician who was blinded to the treatment groups.

The incidence of side-effects such as nausea/vomiting and itching were recorded.

At delivery neonatal outcome including Apgar scores at 1 and 5 minutes, cord blood gas analysis and the Neurologic and Adaptive Capacity Score (NACS) was recorded.[14] The NACS was performed at 15 minutes and 2 hours after delivery. The need for oxygen and neonatal requirement for naloxone were also recorded. Both maternal and cord blood samples were obtained to measure opioid concentrations.

If labour failed to progress (first or second stage) oxytocin was given, according to the hospital protocol.

A ventilatory frequency < 8/min, SpO_2 <90% for >15 s and not being resolved with oxygen, and a maternal heart rate < 50 beats/min were considered serious adverse events, in which case the patient was withdrawn from the study.

For safety reasons, the observer collecting the data was present in the delivery suite at all times until discontinuation of the study medication.

For sample size calculation, we hypothesized that average pain scores in the remifentanil or fentanyl group would differ at least 10% from the meperidine group. Assuming a SD of 15 mm based on previous studies, we calculated a sample size of

sixty parturients per group for a power of 0.95 and a two-sided alpha level of 0.05 to detect this difference. Data analysis was per-protocol. Numerical variables between the groups were compared using the two-tailed Kruskall-Wallis test and *post-hoc* Dunn's multiple comparison test; categorical data were analyzed using the Chi square test. Intragroup comparisons were made using the two-tailed Wilcoxon matched-pairs signed-ranks test. $P<0.05$ was considered statistically significant.

RESULTS

One hundred and eigthy parturients were enrolled of which 159 parturients completed the study: 52 received remifentanil, 53 received meperidine and 54 received fentanyl. Twenty-one parturients were excluded because they delivered within one hour after randomisation (Table 1).

The characteristics of the parturients did not differ statistically. Details of the three groups are listed in Table 2. Duration of labour, oxytocin use and the incidence of nausea/vomiting did not differ between the three groups. Itching occurred more frequently in group R (16%) compared with group P (6%) and F (2%). Significantly more parturients crossed over to epidural analgesia in group P (34% versus 13% in group R and 15% in group F). In group F, significantly more parturients delivered spontaneously (85% versus 62% in group R and 69% in group P). Differences in instrumental delivery and caesarean section rate were not statistically significant.

Table 1. Enrolled: 180 parturients. FCD, full cervical dilatation; EOS, end of study because of full cervical dilatation/delivery, progression to C-section or change to epidural analgesia

	Meperidine: 60	Fentanyl: 60	Remifentanil: 60
FCD<1 h	7	6	8
In study at 1 h	53	54	52
1 h, EOS<2 h	22	15	14
In study at 2 h	31	39	38
2 h<EOS<3 h	14	16	11
In study at 3 h	17	23	27
3 h<EOS<4 h	6	10	8
In study at 4 h	11	13	19
4 h<EOS<5 h	5	5	7
In study at 5 h	6	8	12
5 h<EOS<6 h	1	2	4
In study at 6 h	5	6	8

Table 2. Patient characteristics and details of labour. Data are means (SD) or proportions (%); NS, not significant; NA, not applicable

	Meperidine	Fentanyl	Remifentanil	*P*-value
Age (yr)	33.6 (5.5)	33.5 (4.1)	33.1 (5.0)	NS
Height (cm)	169 (6.7)	169 (6.8)	169 (7.7)	NS
Weight (kg)	84 (14)	79 (12)	81 (13)	NS
Primiparity (%)	35/53 (66)	36/53 (68)	30/52 (58)	NS
Gestation (weeks)	40	40	40	NS
Cervical dilation (cm)	3.6 (1.4)	3.7 (1.3)	4.1 (1.7)	NS
Duration first stage of labour (min)	293 (155)	348 (175)	363 (191)	NS
Duration second stage of labour (min)	42 (35)	38 (26)	36 (30)	NS
Oxytocin used (%)	26/37 (70)	36/51 (71)	33/47 (70)	NS
Spontaneous delivery (%)	24/35 (69)	39/46 (85)	28/45 (62)	<0.05
Instrumental delivery (%)	8/35 (23)	6/46 (13)	10/45 (22)	NS
Caesarean section (%)	3/35 (9)	1/46 (2)	7/45 (16)	NS
Crossover to epidural analgesia (%)	18/53 (34)	8/54 (15)	7/52 (13)	<0.05
Itching (%)	3/51 (6)	1/50 (2)	8/51 (16)	<0.05
Nausea/vomiting (%)	23/51 (45)	20/51 (39)	20/51 (39)	NS
Opioid administered (mg)	133 (50)	0.632 (0.263)	1.84 (1.09)	NA
Duration of treatment (min)	187 (122)	200 (99)	234 (136)	NS

There was no difference in baseline pain scores between the three groups. In all groups, pain scores decreased significantly from baseline 1 hour after the start of treatment. After the first hour, pain scores started to return towards baseline in all groups. At 2 hours, pain scores in group P were not significantly different from baseline. Three hours after the initiation of treatment, pain scores were not significantly different from baseline in any of the groups.

Intergroup comparison showed that the decrease in pain scores after 1 hour was significantly greater in group R [-3.2 (SD 2.9) cm] compared with group F [-1.4 (SD 2.4) cm] and group P [-0.8 (SD 2.2) cm]. After 2 and 3 hours, the decrease in pain scores did not differ significantly between the three groups. Data on pain scores are summarized in Table 3 and Figure 1.

Table 3. Intra- and intergroup comparison pain. Data are means (SD). NS, not significant; R *vs* P, remifentanil *vs* meperidine; R *vs* F, remifentanil *vs* fentanyl; P *vs* F, meperidine *vs* fentanyl; DELTA, change in VAS score relative to the VAS score at inclusion

	Meperidine	Fentanyl	Remifentanil	*P*-value
Intragroup				
VAS at inclusion	7.41 (1.5), *n*=53	7.40 (1.6), *n*=54	7.8 (1.6), *n*=52	
VAS at 1 h	6.61 (2.3), *n*=53	5.96 (2.5), *n*=54	4.56 (2.4), *n*=52	
P VAS 1 vs VAS 0	<0.02	<0.001	<0.0001	
VAS at 2 h	6.78 (2.3), *n*=31	6.47 (2.2), *n*=39	5.70 (2.7), *n*=38	
P VAS 2 vs VAS 0	NS	<0.05	<0.001	
VAS at 3 h	7.19 (1.7), *n*=17	7.26 (2.3), *n*=23	7.16 (2.1), *n*=27	
P VAS 3 vs VAS 0	NS	NS	NS	
Intergroup				
VAS at inclusion	7.41 (1.5), *n*=53	7.40 (1.6), *n*=54	7.8 (1.6), *n*=52	NS
DELTA VAS 1 h	-0.8 (2.2), *n*=53	-1.4 (2.4), *n*=52	-3.2 (2.9), *n*=52	R *vs* P, <0.001; R *vs* F, <0.01; P *vs* F, NS
DELTA VAS 2 h	-0.5 (2.8), *n*=31	-0.9 (2.6), *n*=39	-2.0 (3.1), *n*=38	NS
DELTA VAS 3 h	-0.1 (2.2), *n*=17	-0.4 (2.6), *n*=23	-0.5 (2.3), *n*=27	NS

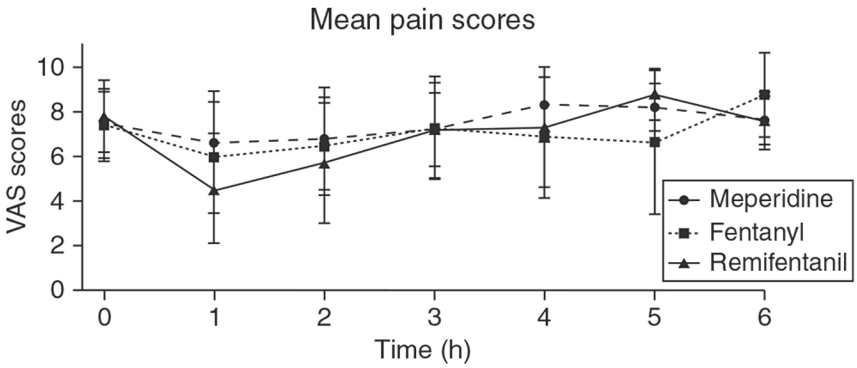

Figure 1. Mean VAS pain scores as a function of time for meperidine, remifentanil, and fentanyl. Vertical bars represent SD.

Sedation scores increased significantly compared to baseline levels during treatment in all groups. The increase in sedation was greatest in group R; after 1 and 2 hours, the increase in sedation in group R was significantly greater compared with groups P and F. After 3 hours, the increase in sedation in group R was significantly greater compared with group F. The differences in sedation scores between group P and F were not statistically significant at any time interval. Data on sedation scores are summarized in Table 4.

There were no differences between the groups in maternal arterial pressure, heart rate and ventilatory frequency. After 1 hour of administration, the decrease in oxygen saturation was greater in group R [-1.13 (2.6)] compared with group P [-0.04 (1.9)]. However, between group R and group F [-0.72 (1.9)] this difference was not significant (Table 5). More parturients in group R (74%) and group F (56 %) experienced one or more periods of desaturation (oxygen saturation < 95%) compared with group P (33%). Six parturients in group R (12%) were administered supplemental oxygen vs four in group P (8%) and one in group F (2%). Data on oxygen saturation are summarized in Tables 5 and 6.

Overall satisfaction, measured after delivery, was greatest in group R [8.1 (1.1) vs 7.0 (1.5) for group P and 7.3 (1.2) for group F], the difference being significant compared with group P (Table 7).

There were no differences in fetal heart rate traces between the three groups. In terms of Apgar score, NACS and fetal cord blood, neonatal outcome was similar in all groups (Table 8).

Table 4. Intra- and intergroup comparison observer sedation. Data are means (SD). NS, not significant; R *vs* P, remifentanil *vs* meperidine; R *vs* F, remifentanil *vs* fentanyl; P *vs* F, meperidine *vs* fentanyl; DELTA, change in observer sedation score relative to the score at inclusion

	Meperidine	Fentanyl	Remifentanil	*P*-value
Intragroup				
Score at inclusion	1.12 (0.3), *n*=53	1.13 (0.3), *n*=54	1.10 (0.3), *n*=52	
Score at 1 h	1.45 (0.5), *n*=53	1.39 (0.5), *n*=54	1.85 (0.8), *n*=52	
P Score 1 vs Score 0	<0.001	<0.01	<0.0001	
Score at 2 h	1.58 (0.6), *n*=31	1.44 (0.6), *n*=39	2.08 (0.8), *n*=38	
P Score 2 vs Score 0	<0.01	<0.05	<0.0001	
Score at 3 h	1.76 (0.6), *n*=17	1.57 (0.6), *n*=23	2.15 (0.8), *n*=27	
P Score 3 vs Score 0	<0.05	<0.05	<0.0001	
Intergroup				
Score at inclusion	1.12 (0.3), *n*=53	1.13 (0.3), *n*=54	1.10 (0.3), *n*=52	NS
DELTA Score 1 h	0.34 (0.6), *n*=3	0.26 (0.6), *n*=54	0.75 (0.8), *n*=52	R *vs* P, <0.05; R *vs* F, <0.01; P *vs* F, NS
DELTA Score 2 h	0.45 (0.7), *n*=31	0.31 (0.7), v39	1.0 (0.9), *n*=38	R *vs* P, <0.05; R *vs* F, <0.01; P *vs* F, NS
DELTA Score 3 h	0.65 (0.8), *n*=17	0.39 (0.7), *n*=23	1.04 (0.9), *n*=27	R *vs* P, NS; R vs F, <0.05; P *vs* F, NS

Table 5. Intra- and intergroup comparison saturation. Data are means (SD). NS, not significant; R *vs* P, remifentanil *vs* meperidine; R *vs* F, remifentanil *vs* fentanyl;
P *vs* F, meperidine *vs* fentanyl; DELTA, change in saturation relative to the saturation at inclusion

	Meperidine	Fentanyl	Remifentanil	*P*-value
Intragroup				
Score at inclusion	97.23 (1.5), *n*=53	97.41 (1.5), *n*=54	97.17 (1.8), *n*=52	
Score at 1 h	97.19 (1.6), *n*=53	96.69 (1.9), *n*=54	96.04 (2.3), *n*=52	
P Score 1 *vs* Score 0	NS	P<0.01	P<0.05	
Score at 2 h	96.88 (1.5), *n*=32	96.66 (2.0), *n*=38	95.76 (2.5), *n*=37	
P Score 2 *vs* Score 0	NS	<0.05	NS	
Score at 3 h	96.67 (1.6), *n*=18	95.86 (1.9), *n*=22	96.45 (1.7), *n*=29	
P Score 3 *vs* Score 0	NS	<0.01	NS	
Intergroup				
Score at inclusion	97.23 (1.5), *n*=53	97.41 (1.5), *n*=54	97.17 (1.8), *n*=52	NS
DELTA Score 1 h	-0.04 (1.9), *n*=53	-0.72 (1.9), *n*=54	-1.13 (2.6), *n*=52	R *vs* P, <0.05; R *vs* F, NS; P *vs* F, NS
DELTA Score 2 h	-0.28 (2.1), n=32	-0.84 (2.1), *n*=38	-1.08 (3.5), *n*=37	NS
DELTA Score 3 h	-0.44 (2.0), *n*=18	-1.5 (2.1), *n*=22	-0.28 (2.3), *n*=29	NS

Table 6. Episodes of maternal oxygen saturation <95% and oxygen supplementation. Data are proportions (%). NS, not significant; R *vs* P, remifentanil *vs* meperidine; R *vs* F, remifentanil *vs* fentanyl; P *vs* F, meperidine *vs* fentanyl

	Meperidine	Fentanyl	Remifentanil	*P*-value
Oxygen administered (%)	4/52 (8)	1/52 (2)	6/51 (12)	NS
Oxygen saturation <95% (%)	16/48 (33)	30/54 (56)	37/50 (74)	R *vs* P, <0.0001; R *vs* F, NS; P *vs* F, <0.05

Table 7. Post-delivery maternal satisfaction score. Data are means (SD). NS, not significant; R *vs* P, remifentanil *vs* meperidine; R *vs* F, remifentanil *vs* fentanyl; P *vs* F, meperidine *vs* fentanyl

	Meperidine	Fentanyl	Remifentanil	*P*-value
Satisfaction scores (1–10)	7.0 (1.5), *n*=30	7.3 (1.2), *n*=42	8.1 (1.1), *n*=38	R *vs* P, <0.05; R *vs* F, NS; P *vs* F, NS

Table 8. Fetal and neonatal characteristics. Data are means (SD) or proportions (%). NS, not significant

	Meperidine	Fentanyl	Remifentanil	*P*-value
Apgar score 1 min	8.6 (0.9), *n*=32	8.5 (1.3), *n*=45	8.9 (0.7), *n*=38	NS
Apgar score 5 min	9.7 (0.6), *n*=32	9.6 (0.8), *n*=45	9.9 (0.3), *n*=38	NS
NACS 15 min	36.8 (2.1), *n*=25	35.9 (3.6), *n*=38	37.0 (2.2), *n*=31	NS
NACS 120 min	37.2 (2.7), *n*=26	36.7 (3.2), *n*=38	7.8 (2.0), *n*=30	NS
Cord blood pH	7.21 (0.1), *n*=30	7.22 (0.1), *n*=39	7.25 (0.1), *n*=37	NS
Cord blood BE	-7.23 (4.5), *n*=27	-6.67 (3.9), *n*=36	-5.41 (2.6), *n*=35	NS
CTG reactive (%)	44/53 (83)	48/54 (89)	44/52 (85)	NS

DISCUSSION

Overall, the decrease in pain scores varied from mild to moderate, average pain scores remaining above 4.5 cm in all groups. Remifentanil PCA performed significantly better than meperidine PCA and fentanyl PCA, but only during the first hour of treatment. Although the decrease in pain scores was greatest in group R at all time intervals, the difference was only significant at 1 hour. In all three groups, pain scores started to increase towards baseline after 1 hour of treatment. Meperidine PCA performed worst, with pain scores not differing significantly from baseline 2 hours after the initiation of treatment, and significantly more parturients crossing over to epidural analgesia. In all three groups, pain scores no longer differed significantly from baseline 3 hours after treatment was started.
Overall satisfaction scores were higher for remifentanil PCA, but remifentanil PCA produced more sedation compared with meperidine PCA and fentanyl PCA.

There have been multiple clinical studies on the use of remifentanil in the parturient.[12 13 15-25] Some studies comparing remifentanil PCA with meperidine showed better results for remifentanil.[13 19 20 22] However, these studies contain relatively small groups of patients; in some studies the observation period was limited and in a number of studies labouring women were allowed to use nitrous oxide concomitantly, which may have affected the results.
Our results are in agreement with Volikas and Male[19] and Evron and colleagues[22], who reported significantly lower pain scores with remifentanil compared with meperidine. Most previous studies only evaluated the first 2 hours of administration of remifentanil. In our study, we assessed pain scores up to 3 hours. This is an important difference with other studies, as we noticed a return towards baseline VAS scores of all three opioids over time, with pain scores returning to pre-treatment levels in all groups after 3 hours of treatment. It should be noted that this observation does not imply a lack of effect as pain scores are known to increase during labour.[26]
The use of a background infusion with intravenous PCA with remifentanil is disputable. The rapid offset of remifentanil does not promote reaching a steady-state plasma concentration when using only intermittent boluses, and from this pharmacokinetic perspective, adding a background infusion would seem rational. However, one study comparing different bolus doses with or without background infusion found bolus doses of 0.25-0.5 μg/kg remifentanil without background infusion most suitable for labour analgesia.[12] In addition, low oxygen saturations with remifentanil were reported in previous studies when using a background infusion.

We therefore chose to use only intermittent boluses. However, our results show that despite the absence of a background infusion, the use of intermittent remifentanil was still associated with episodes of maternal desaturation (oxygen saturation < 95%).
We limited the total dose of meperidine to 200 mg, as this is considered to be the maximum dose used in Dutch obstetric units. While it may be argued that this dose limit is conservative, none of the parturients in the meperidine group reached the maximum dose limit in the 5 hour time frame that resulted from our dosing regime. Five parturients reached the maximum dose limit, all of them beyond the 5 hour time frame (385 – 500 min). We therefore do not believe that our dosing regime adversely affected outcome in the meperidine group.
The most concerning adverse effect of i.v. opioids on the labour ward is respiratory depression. During administration of remifentanil, the decrease in oxygen saturation was significantly greater when compared with meperidine; during the first 2 hours of treatment, the use of remifentanil was associated with significantly more sedation when compared with fentanyl and meperidine. Although these side effects will be quickly reversible considering the short half-life of remifentanil, a high level of sedation and periods of desaturation are undesirable side effects during labour.
There was no difference in neonatal outcome between the groups. This is an important finding, as it would be expected that over time remifentanil would have less effect on the neonate compared with longer-acting agents such as meperidine or fentanyl.
Interestingly, we found that significantly more parturients receiving fentanyl PCA delivered spontaneously when compared with the women receiving either meperidine or remifentanil PCA; the explanation for this finding is unclear and further study is required to establish whether this significance is spurious or valid.

In conclusion, under the conditions of our study, remifentanil PCA was more effective than meperidine and fentanyl PCA in providing pain relief during labour, but it was associated with significantly more sedation and itching compared with both other opioids and more periods of maternal oxygen saturation decreasing below 95% compared to meperidine. Its effectiveness was time-limited (2h), therefore we would recommend the use of remifentanil only in the last phase of cervical dilation. Because remifentanil is a potent respiratory depressant, continuous monitoring is required. Further studies are needed to determine the safety of remifentanil especially with relation to its respiratory effects.

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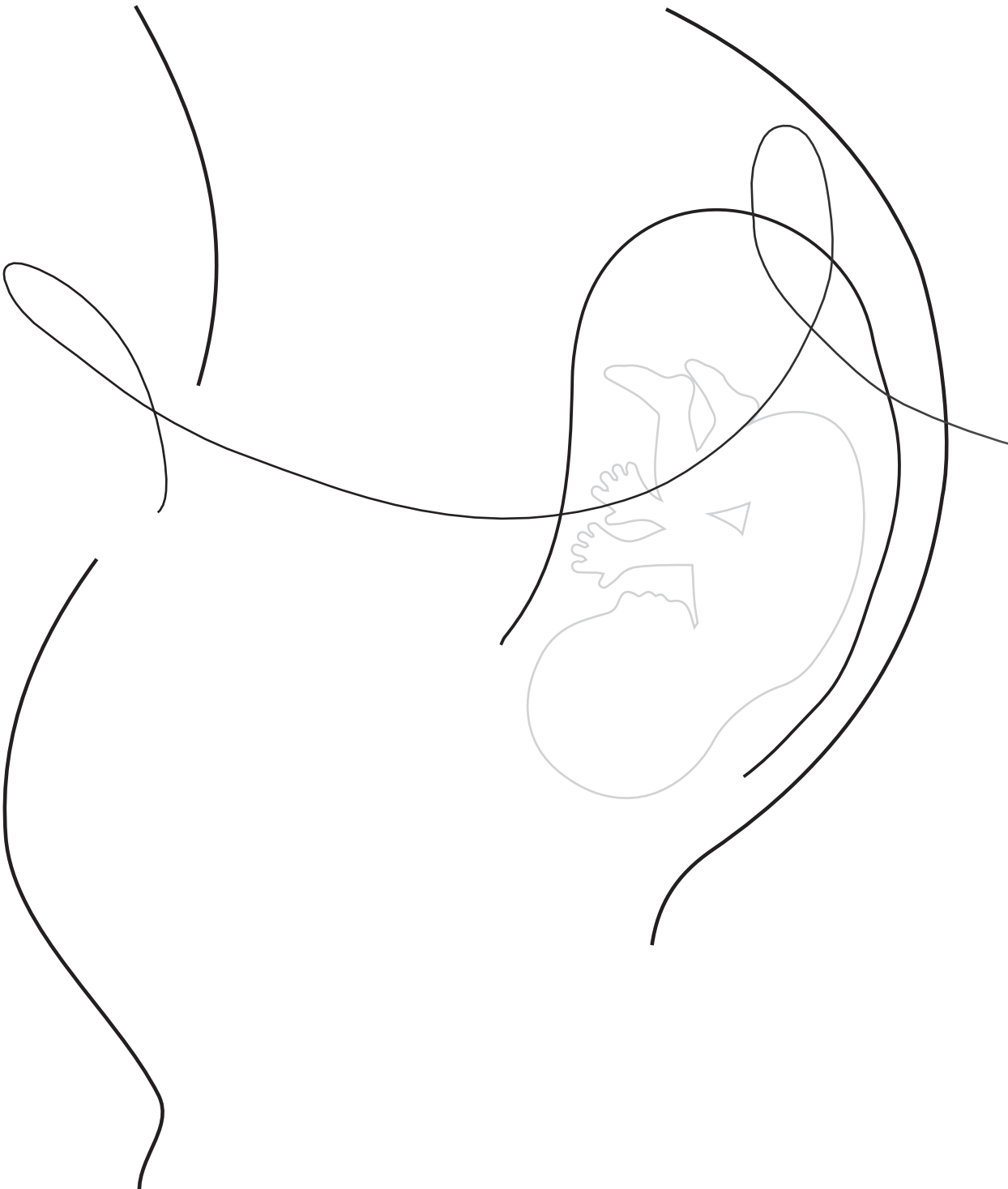

Chapter 3

A randomised comparison of intravenous remifentanil patient-controlled analgesia with epidural ropivacaine/sufentanil during labour

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INTRODUCTION

Epidural analgesia is considered to be the most effective method of pain relief during labour. However, its use may be contraindicated or parturients may prefer less invasive treatment, so alternative methods of pain relief may be required.

Remifentanil, a μ-opioid agonist, has a rapid onset and offset, which are suitable characteristics for patient-controlled analgesia (PCA). The opioid has a short context-sensitive half-life (3-4 min) and elimination half-time of 10-20 min.[1,2] Compared to other systemically administered opioids, the short half-life makes remifentanil an attractive option for labour analgesia. A recent study from our unit compared labour analgesia with remifentanil, fentanyl or meperidine PCA. Remifentanil produced only moderate pain relief that was associated with a return of pain scores to baseline within three hours of treatment.[3] Two studies have compared the efficacy of remifentanil to epidural analgesia, although both have limitations. Volmanen limited the observation period to 1 h,[4] whereas El-Kerdawy recorded pain scores before analgesia, 1 h after analgesia, and post delivery.[5]

The main objective of this prospective, randomised study was to compare the efficacy of remifentanil PCA with epidural analgesia. Secondary objectives were to compare maternal side effects and neonatal outcome.

METHODS

The study protocol was approved by the local Research Ethics Committee. Written informed consent was obtained in the antenatal clinic or before the onset of active labour. Twenty healthy parturients (ASA I or II) in active labour with singleton cephalic presentation and without prior use of opioid analgesics were recruited. Exclusion criteria included cervical dilation >5 cm, preeclampsia, insulin-dependent diabetes, substance abuse, opioid allergy and morbid obesity (body mass index ≥ 40 kg/m^2). The protocol for remifentanil PCA or epidural analgesia was contained in numbered envelopes that had been randomised using a computer-generated random sequence. Parturients randomised to the intravenous remifentanil group received a 40-µg loading dose and boluses of 40 µg with a 2-min lockout time and bolus duration of 36 s using a Graseby 3300 syringe pump (Smiths Medical International, Ashford, Kent, UK). Maximum dose limit was 1200 µg/h. This dose regimen was based on previous studies.[6 7] Parturients were instructed how to use the PCA device, but no specific advice was given concerning use at the beginning of uterine contraction. If pain relief was inadequate at any time, the patient could request epidural analgesia. In most obstetric units in The Netherlands, remifentanil is not continued into the second stage of labour for fear of possible neonatal depression, therefore the PCA device was discontinued when parturients reached full cervical dilation. No further analgesia was provided during the second stage.

Women randomised to receive epidural analgesia were prehydrated with 500 mL intravenous crystalloid solution before an epidural catheter was placed using a midline approach with a 17-gauge Tuohy needle and loss-of-resistance to saline at L2-3 or L3-4. A loading dose of 0.2% ropivacaine 12.5 mL was given through the epidural catheter, followed by a continuous infusion of ropivacaine 0.1% with sufentanil 0.5 µg/mL at 10 mL/h. If analgesia was inadequate, additional boluses of the epidural solution were given. At full cervical dilation the epidural infusion was discontinued according to local hospital policy.

Baseline non-invasive measurements before treatment included maternal blood pressure, heart rate and pulse oximetry. Maternal oxygen saturation was monitored continuously. Measurements were recorded every 5 min for the first 30 min, and then every 30 min until delivery. Hypotension (systolic blood pressure <90 mmHg or >25% below baseline) was treated with intravenous fluids and intravenous ephedrine 5 mg or phenylephrine 100 µg. Supplemental oxygen was administered if maternal oxygen saturation (SpO_2) levels remained below 95 % for more than 60 s.

Pain scores were assessed using the visual analogue scale (VAS) method ranging

from 0 (no pain) to 10 cm (worst pain imaginable). Women were asked to record pain during contractions every hour, starting with a baseline score before treatment. At the same time intervals, women were asked to record their satisfaction with analgesia and comfort on a VAS satisfaction score, where 0 corresponded with highly dissatisfied and 10 with highly satisfied. A sedation score (1= awake, 2=sleepy, 3=eyes closed, but rousable by vocal stimulus, 4= eyes closed, but rousable by physical stimulus, 5= unrousable) was assessed every hour by the observer. The incidence of nausea, vomiting and itching was recorded. After delivery parturients were asked to express their overall satisfaction with pain relief during the first and second stages of labour, and of delivery, on a ten-point numerical scale ranging from 1 (highly dissatisfied) to 10 (highly satisfied).

Fetal heart rate and uterine activity were measured continuously by external monitoring. Fetal scalp electrode and intra-uterine pressure recording were used when deemed necessary by the attending obstetrician. Fetal heart rate patterns were scored as reactive or non-reactive by an obstetrician who was blinded to study allocation. After delivery, Apgar scores were recorded at 1 and 5 min and umbilical cord blood gas analysis was performed.

Serious adverse events were considered to be a maternal respiratory rate of < 8 breaths/min, maternal SpO_2 less than 90% for more than 15 s unresolved with oxygen and a maternal heart rate <50 beats/min. If such an event occurred the patient was withdrawn from the study. Observers collecting study data were present in the delivery room at all times during treatment in both groups.

Statistical analysis

The primary outcome parameter of this study was the VAS pain score. Secondary outcome measures included maternal satisfaction scores, sedation scores and SpO_2. For sample size calculations, we assumed a reduction in VAS pain scores to 5 in the remifentanil group based on previous studies, whereas with epidural analgesia pain scores decrease to 0–2. Assuming a standard deviation (SD) of 2, we calculated that a group size of 10 subjects would be sufficient to detect a difference of 3 in VAS scores (power = 0.9, two-sided alpha level = 0.05). Data analysis was per protocol. Data are presented as mean (SD), or proportions as appropriate. Numerical variables between groups were compared using the two-tailed Mann-Whitney-U test; comparisons within groups were made using the two-tailed Wilcoxon matched-pairs signed-ranks test. Categorical data were compared using Fisher's exact test. A P value <0.05 was considered statistically significant.

RESULTS

Twenty-six parturients were enrolled of whom 20 completed the study; 10 subjects received remifentanil, 10 received epidural analgesia. Six parturients were excluded because of either delivery within one hour of randomisation (n = 5) or unsuccessful placement of the epidural catheter (n = 1) (Fig 1). Demographic and treatment characteristics of the parturients were similar (Table 1). One parturient in the remifentanil group requested epidural analgesia after 2 h and her data for maternal satisfaction, pain scores after 2 h and neonatal outcome were excluded from analysis. No serious adverse events were observed in any patient.

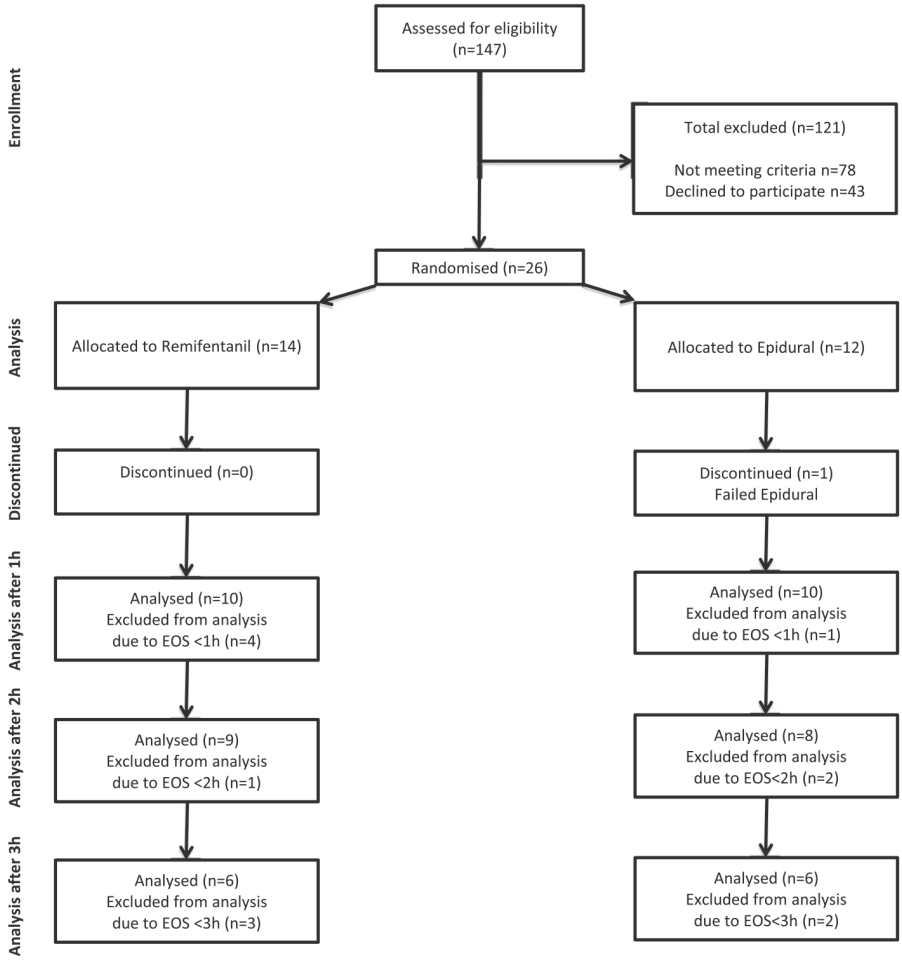
Baseline pain scores were similar in both groups. After 1 h, pain scores decreased significantly in both groups. After 2 h, pain scores in the remifentanil group increased and were no longer significantly different from baseline scores. By contrast, epidural pain scores remained significantly lower than baseline after 2 and 3 h. Intergroup comparison showed that the decrease in pain scores in the epidural group was significantly larger at all time intervals compared to the remifentanil group. Data on pain scores are summarized in Fig 2 and Table 2.

After 1 h of treatment, mean SpO_2 was significantly lower in the remifentanil group compared to the epidural analgesia group (95.2 ± 2.4 % vs. 99.0 ± 1.1 %, $p<0.01$). Intergroup comparison showed that the decrease in SpO_2 was significantly greater in the remifentanil group after 1 and 3 h of treatment (Table 2). No patient in the epidural group and one patient in the remifentanil group received supplementary oxygen.

There were no differences in average instrumental or caesarean delivery rates between the groups (Table 1). More patients receiving remifentanil experienced nausea and vomiting (5/10 and 5/10 respectively) than patients receiving epidural analgesia (2/10 and 1/10 respectively), but this was not statistically significant (Table 2). No maternal hypotension or bradycardia was observed. Patient satisfaction scores during labour and 2 h after delivery were similar. Sedation was minimal and there were no differences between the two groups.

There were no differences between the groups in cardiotocograph (CTG) readings, average Apgar score, umbilical artery pH and base excess (Table 3). Following administration of analgesia, the CTG was reactive in eight of the remifentanil group and seven of the epidural group. Two neonates in the remifentanil group had a pH <7.0. One was born spontaneously 60 min after remifentanil had been discontinued. The other was born with a forceps extraction after failed ventouse and was admitted to Neonatal Intensive Care Unit with suspected infection. Study medication had been stopped 110 min before birth.

Three neonates had 1 min Apgar scores <7, one in the remifentanil group and two in the epidural group. One neonate in the epidural group was born following forceps extraction for acute fetal distress, and had Apgar scores of 4 and 5 at 1 and 5 min, respectively. The baby was subsequently diagnosed with nemaline myopathy. The other neonate was born after a ventouse delivery due to acute fetal distress and had Apgar scores of 6 and 8 at 1 and 5 min, respectively.



* EOS = End of study because of full cevical dilatation/delivery, progression to caesarean section or crossover to epidural.

Figure 1. Participant flow through the randomised trial.

Table 1 Maternal and labour characteristics

	Remifentanil (n = 10)	Epidural (n = 10)
Age (years)	32.7 (5.9)	31.0 (5.2)
Height (cm)	168.4 (9.4)	168.0 (7.6)
Weight (kg)	83.3 (16.7)	78.9 (11.9)
Primiparity	5	7
Cervical dilation at onset of analgesia (cm)	4.2 (1.1)	3.6 (1.3)
Duration first stage of labour (min)	488 (277)	410 (173)
Duration second stage of labour (min)	71 (40)	32 (14)
Duration of analgesia (min)	286 (145)	269 (142)
Oxytocin for augmentation of labour	9	10
Delivery		
Spontaneous	7	4
Instrumental	1	4
Caesarean	2	2
Crossover to epidural analgesia	1	NA
Remifentanil administered (µg)	2817 (1564)	NA
Ropivacaine administered (mg)	NA	69.8 (23.7)
Sufentanil administered (µg)	NA	22.4 (11.9)

Data are mean (SD) and *n*.
No significant differences between groups.

Table 2 Maternal pain scores and side effects

	Remifentanil (n = 10)	Epidural (n = 10)	P value
VAS scores			
0 h	7.8 (1.6)	8.4 (0.9)	NS
1 h	4.0 (2.0)*	1.6 (2.2)*	<0.05
2 h	6.7 (1.5)	1.7 (1.3)*	<0.01
3 h	5.7 (3.0)	1.4 (1.0)*	<0.05
Maternal SaO_2			
0 h	98.0 (1.6)	98.7 (1.6)	NS
1 h	95.2 (2.4)†	99.0 (1.1)	<0.01
2 h	96.8 (1.7)	98.6 (1.3)	NS
3 h	95.5 (3.3)	99.1 (0.7)	<0.05
Maternal satisfaction scores			
1 h	8.6 (1.1)	8.3 (1.5)	NS
2 h	7.4 (1.8)	8.6 (0.9)	NS
3 h	7.3 (0.8)	7.3 (0.8)	NS
after delivery	8.0 (1.3)	8.3 (0.9)	NS
Sedation scores			
0 h	1.1 (0.3)	1.1 (0.3)	NS
1 h	1.4 (0.5)	1.3 (0.5)	NS
2 h	1.4 (0.5)	1.3 (0.5)	NS
3 h	1.7 (0.8)	1.3 (0.5)	NS
Maternal side effects			
Itching	2	3	NS
Nausea	5	2	NS
Vomiting	5	1	NS

Data are mean (SD); NS not significant.
* P <0.01 compared to 0 h; † P <0.05 compared to 0 h; NS not significant.

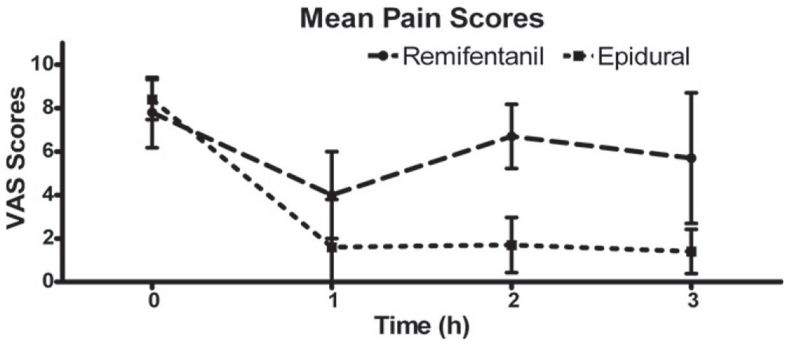


Figure 2. Mean VAS pain scores as a function of time for remifentanil and epidural analgesia. Vertical bars represent SD.

Table 3 Neonatal outcome

	Remifentanil (n = 7)	Epidural (n = 8)	P value
Apgar scores			
1 min	8.3 (1.3)	7.5 (1.9)	NS
5 min	9.3 (1.0)	8.9 (1.7)	
<7 at 1 min	1	2	
<7 at 5 min	0	1	
Umbilical artery pH	7.14 (0.1)	7.19 (0.1)	NS
Umbilical artery base excess	-11.1 (4.6)	-8.8 (2.4)	NS

Data are mean (SD) or n.; NS: Not significant.
Data from women who required caesarean section or who crossed over to epidural analgesia were excluded.

DISCUSSION

This study shows epidural analgesia is more effective at reducing pain scores than intravenous remifentanil PCA. Pain scores with epidural analgesia were significantly lower, and had a longer duration of action. These results confirm our earlier work, in which pain scores returned to pre-treatment levels within 3 h of administration of remifentanil.[3] The initial decrease and subsequent increase in pain scores has been observed before,[8] and may be caused by greater pain as labour progresses, tolerance to remifentanil, or both. It may be appropriate to increase the remifentanil dose over time to overcome this problem.

Comparisons of remifentanil and epidural analgesia have been made in earlier studies.[4 5 9] Evron et al.[9] focused primarily on the effect of remifentanil or acetaminophen with epidural ropivacaine on maternal temperature. VAS pain scores were not an outcome parameter, although average pain scores were significantly lower in patients receiving epidural ropivacaine compared to those receiving only intravenous remifentanil. Volmanen had similar findings,[4] but the observation period was limited to the first hour of treatment. El Kerdawy and Farouk found no difference in pain scores between epidural bupivacaine/fentanyl and PCA remifentanil.[5] The duration of analgesic treatment was not reported, but VAS pain scores were recorded at only three points: a baseline score before starting analgesia, 1 h after starting treatment, and after delivery. Since VAS pain scores were not recorded at other times during labour, and the post-delivery score was an overall retrospective assessment, the comparison between epidural analgesia and remifentanil in this study was effectively limited to 1 h.

In the current study, satisfaction scores were not statistically different between the groups, which seems inconsistent with the difference found in pain scores. Since our power analysis was based on pain scores during the first stage of labour, a type II error may cause the absence of a statistically significant difference in maternal satisfaction scores; larger groups are necessary to evaluate this. Increased pain tolerance resulting from the sedative and euphoric effects of opioids,[10] especially in women,[11] may also have contributed.

Volmanen compared epidural levobupivacaine and fentanyl with intravenous remifentanil analgesia. Pain scores were better for epidural analgesia, but no difference was found in satisfaction scores between treatments. This was attributed to the use of an 'ultra dilute' epidural solution.[4] However, our study used a higher concentration of local anaesthetic and the same inconsistency between relatively high pain scores and high satisfaction scores with remifentanil was noted.

Sedation scores were not different between the groups, in contrast to other studies

that have shown increased sedation with remifentanil PCA.[3 4 12] The current study was not powered to detect differences in sedation and hence the sample size may have been too small to detect such an effect. The observer scale used to determine sedation may also be less sensitive compared with subjective scales. When asked to note sedation while using remifentanil, patients reported an increase (from 2 to 6 on a 10-point VAS scale), while external observers reported a smaller increase (from 1 to 2 on a 5-point scale).[6]

Remifentanil PCA was associated with a significant decrease in maternal SpO_2 after 1 h of treatment. The difference in SpO_2 between the two groups was significant after 1 and 3 h. The clinical relevance of this finding is limited, as only one parturient in the remifentanil group met the criteria for supplemental oxygen. However, the study was not powered to detect differences in SpO_2 or the need for supplemental oxygen, for which a larger sample size would be required.

There was no difference in the incidence of nausea and vomiting between the groups, which corresponds with results from other studies.[4 13]

There were also no differences in neonatal outcome. Two neonates in the epidural group and one in the remifentanil group had low Apgar scores. If the neonate with undiagnosed nemaline myopathy is excluded, all Apgar scores were normal five minutes after delivery. Two neonates were born with umbilical arterial pH <7.0 in the remifentanil group, but in both cases remifentanil had been discontinued at least one hour before delivery, making a causal relationship unlikely.

Since the study was powered to detect a difference of 3 in VAS pain scores, the small sample size makes interpretation of secondary outcomes difficult. The number of patients who achieved full cervical dilatation during the first hour of remifentanil analgesia, and hence received no further analgesia in the second stage of labour, also compounds the limitation.

In conclusion, epidural analgesia with ropivacaine and sufentanil provided better and more continuous analgesia during labour compared to intravenous remifentanil PCA. Remifentanil was associated with lower maternal oxygen saturation at 1 h. Continuous monitoring of maternal SpO_2 and respiratory rate is recommended until safety of remifentanil regimens can be confirmed.

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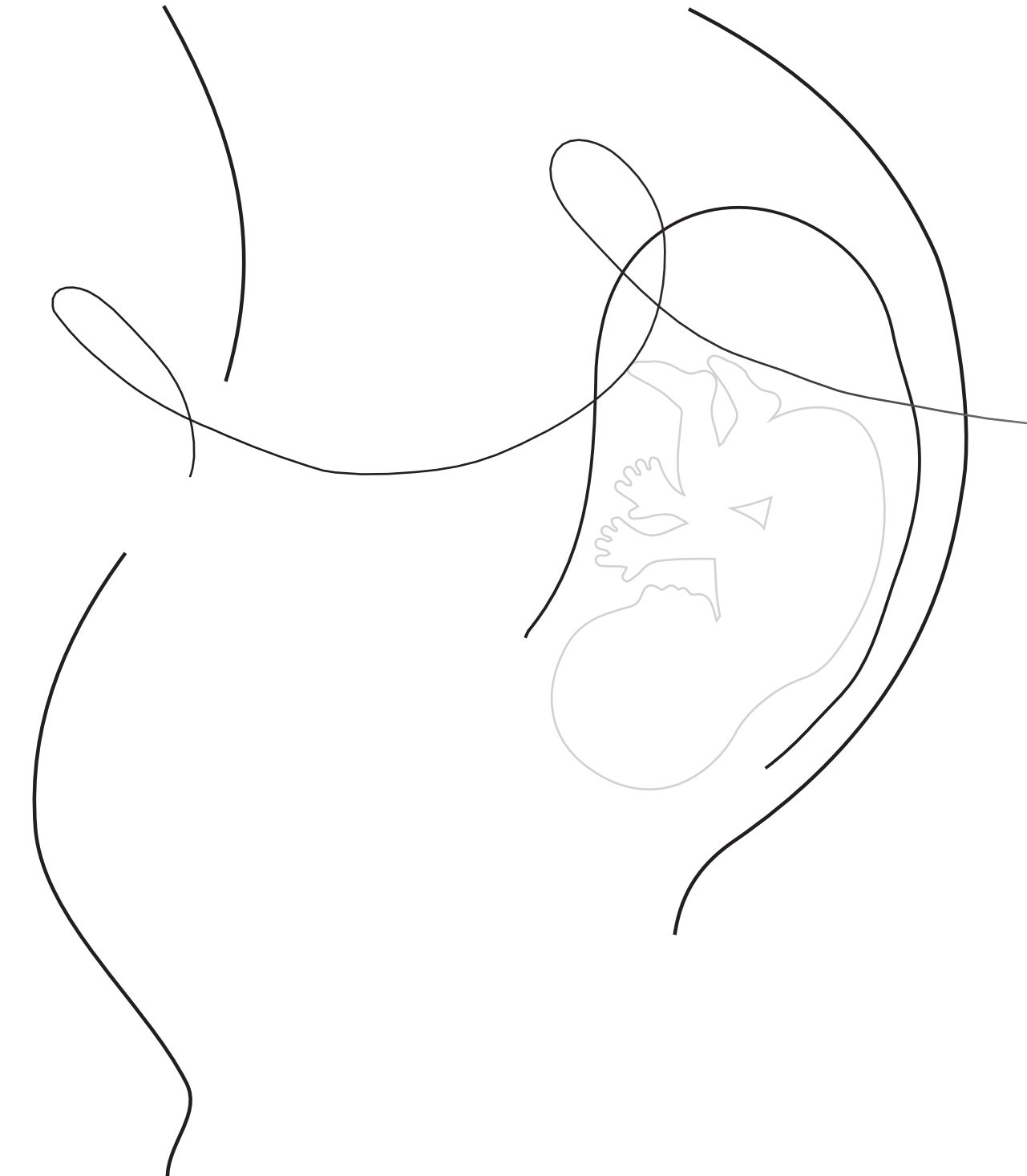
Chapter
3



Chapter 4

Differences in maternal temperature during labour pain treatment with remifentanil PCA or epidural analgesia: a randomised controlled trial

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INTRODUCTION

Epidural analgesia (EA) offers effective and safe analgesia during labour. However, in some cases its use may be contraindicated. One disadvantage of the technique is a possible increase in maternal temperature,[1-4] which frequently results in the unnecessary administration of antibiotics during labour and the presumed diagnosis and treatment of neonatal sepsis.[3] The mechanism of maternal hyperthermia during EA remains unclear. It is suggested that EA leads to an alteration of maternal thermoregulation in parturients,[1] or that fever during labour is a normal manifestation that is suppressed in patients receiving opioids but not in patients receiving EA.[5] If true, the increased incidence of hyperthermia during labour is not a complication of the technique.

An alternative to EA is intravenous remifentanil. Remifentanil, a μ-opioid receptor agonist, has a rapid onset of action and short latency to peak analgesic effect, rendering it suitable for patient controlled analgesia (PCA). Placental transfer occurs, but there is rapid metabolism and redistribution in the neonate.[5] There has been a substantial increase in the use of remifentanil during labour. Adverse effects resemble those of other potent opioid analgesics and include respiratory depression with oxygen desaturation and sedation. Clinical studies on the use of remifentanil in the parturient show better efficacy (i.e., pain intensity score reduction) for remifentanil compared to meperidine.[6-8] However compared to EA, analgesic efficacy is inferior.[9-11] Furthermore, there are concerns about remifentanil's safety with respiratory depression and sedation as potential risks.[11, 12]

The primary objective of this randomised, controlled trial was to compare the incidence of maternal fever (temperature ≥ 38 °C) in parturients receiving intravenous remifentanil by patient-controlled analgesia (RPCA), with parturients receiving either EA or no analgesia. We hypothesised that fever is more prevalent in patients receiving EA compared to patients on either RPCA or patient receiving no analgesia. Secondary objectives included differences in maternal oxygen saturation (SpO_2), nausea, vomiting, sedation, pruritus, hypotension and neonatal outcome.

METHODS

This study was performed at the Leiden University Medical Center after obtaining approval from the local Research Ethics Committee. The trial was registered under number NTR1498 (www.trialregister.nl). Written informed consent was obtained either in the antenatal clinic or in the obstetrics ward before active labour (regular contractions leading to dilation of the cervix) started. ASA I or II parturients with a singleton pregnancy, between 37 and 42 weeks of gestation were considered eligible to participate. Exclusion criteria included body mass index ≥ 40 kg/m^2, insulin dependent diabetes, severe pre-eclampsia (proteinuria ≥ 5 g/24h), use of antibiotics during delivery, initial maternal SpO_2 < 98%, initial maternal temperature ≥ 38°C, cervical dilation of >7 cm and ruptured membranes for more than 24 hours at the time of inclusion. If delivery occurred within 1 hour after the study start, women were excluded from analysis.

This is a two-arm randomised controlled trial with a third-arm observational cohort. All eligible parturients that were admitted to the obstetrics unit in spontaneous labour or undergoing induction of labour and who consented to participate initially entered the study as control group. Women requesting analgesia were subsequently randomised to either RPCA or EA. Parturients who did not request analgesia during labour and delivery remained in the control group. Randomisation was performed using a computer generated randomisation list and treatments (RPCA or EA) were presented in a numbered opaque sealed envelope that was opened upon the request for analgesia. For purposes of the study, the time that the patients entered the labour ward was considered t=0. However, for patients that at one point requested pain relief, the moment of request was taken as t = 0.

Patients in the RPCA group received 40 µg infusions (lockout time of 2 min, infusion duration of 36 s) using a PCA device (Graseby 3300 syringe pump, Smiths Medical Int., UK). The maximum dose permitted was 1200 µg/h. No background infusion was added. The specific dose regime for remifentanil was based on previous studies.[13, 14] Because of concerns about the potential for neonatal respiratory depression, the pump was stopped when parturients reached full cervical dilatation. When parturients were dissatisfied with the analgesic effect, EA was offered as alternative.

In case of randomisation to EA, a catheter was inserted at the L2 or L3 interspace using a 17-gauge Tuohy needle. Parturients received a loading dose of 25 mg ropivacaine (12.5 mL ropivacaine 0.2%), followed by a continuous infusion of a solution containing ropivacaine 0.1% and sufentanil 0.5 µg /mL (infusion rate 10 mL/h). In case of inadequate analgesia, additional 10 mL boluses could be given. In case of

epidural catheter dislodgement, the catheter was replaced. Maternal SpO_2 and heart rate (HR) were monitored continuously using a WristOx 3100 (Nonin Medical, Amsterdam, The Netherlands). Each 4 s one data point was obtained that was stored on a computer for further analysis. When SpO_2 dropped <92% for more than 60 s, oxygen was administered by facemask. Maternal temperature was measured hourly using a calibrated tympanic thermometer (Genius 2, Covidien, Minneapolis, MN, USA). Intrapartum fever was defined as maternal tympanic temperature ≥ 38 °C (100.4 °F). In case of fever, antibiotics could be provided to the parturient. However, this was left to the discretion of the attending obstetrician as no specific guidelines regarding treatment of fever during labour exist in the Netherlands. In case of maternal antibiotic treatment the neonate was admitted and treated.

Maternal blood pressure and respiratory rate (RR) were measured hourly until delivery. In parturients receiving RPCA or EA, blood pressure and RR were recorded every five min for the first 30 min following initiation of analgesic treatment. Hypotension (systolic blood pressure < 90 mmHg or > 25% below pre-analgesia values) was treated with intravenous fluids and/or intravenous ephedrine or phenylephrine.

A visual analogue scale (VAS) was used to assess pain intensity scores, experienced during contractions, ranging from 0 (no pain) to 10 cm (worst pain imaginable); measurements were obtained hourly. An observer sedation score (1 = awake, 2 = sleepy, 3 = eyes closed, but rousable by vocal stimulus, 4 = eyes closed, but rousable by physical stimuli, 5 = unrousable) was recorded every hour. Parturients were asked if they experienced any nausea/vomiting or itching.

Fetal heart rate (HR) and uterine activity were measured continuously by an external monitor. When data were difficult to interpret or complications (eg. meconium stained amniotic fluid) occurred, invasive monitoring by means of scalp electrode and/or intra-uterine pressure recording was instituted. Every hour, fetal HR was recorded and fetal HR patterns were scored as reactive or not reactive. Neonatal outcomes including Apgar scores at 1 and 5 min, cord blood gas analysis, naloxone use, neonatal fever (>38 °C within 24 h of birth) and need for oxygen were recorded. If labour failed to progress oxytocin was administered according to hospital protocol.

After delivery, parturients were asked to give an overall satisfaction score on pain relief during labour. The score ranged from 1 (highly dissatisfied) to 10 (highly satisfied). Severe adverse events were a reason to discontinue analgesia and to abort the study. We considered the following circumstances severe adverse events: RR <8 breaths/min, SpO_2 <90% for more than 15 s, which was not resolved with oxygen.

Statistical analysis

The primary outcome variable was the proportion of women who developed fever (T ≥ 38 °C (100.4 °F)) before delivery. With a chosen *P* <0.05 and a power of 0.80, the population size was calculated using the smallest expected difference. With the assumption of an 18% difference in the incidence of intrapartum fever (23% EA versus 5% RPCA),[15] the sample size of the trial was calculated to be 175, of which 116 would be randomised between the epidural and remifentanil groups.

Data were analysed using an intention-to-treat-analysis. In case of crossover, data acquisition continued. Analysis of continuous data was performed using the Kruskall-Wallis test. Categorical data were analysed using the Pearson chi square-test. Values are mean ± SD. To derive a prognostic model for the occurrence of a clinically relevant increase in temperature (T ≥ 38 °C), several factors beside mode of analgesia, were considered as potential prognostic variables. Crude risks and 95% confidence intervals (CIs) of all factors were calculated by univariable logistic regression. Determinants were further tested if, in the univariable analysis , two-sided P values were less than 0.10 and/ or if the variable was deemed relevant (from a clinical or biological point of view) These determinants were tested by multivariable logistic regression with backward selection (*P* value 'In' 0.05, *P* value 'Out' 0.10). With respect to mean temperature, we added a post-hoc test (ANOVA) to identify which group differed from the other two groups, with Bonferroni correction to manage multiple comparisons. Data were analysed using SPSS 19 (SPSS, Chicago, IL, USA).

RESULTS

We assessed the eligibility of 250 women, of whom 164 were enrolled in the study (Fig. 1). After inclusion of 116 parturients in the two treatment groups, further inclusion was stopped; the control group included 48 parturients. After excluding women who delivered within 1 hour, 140 women were analysed, 49 on RPCA, 49 on EA and 42 in the control group. Due to technical difficulties continuous saturation data were not always available and this information is reported for only 114 women. Therefore this result is reported for only 114 women. Details of maternal and labour characteristics are reported in Table 1. In the control group, there were more multiparous women and the duration of labour in the first and second stage was significantly shorter in this group compared to the other two treatments. Crossover occurred in 17% (8/49) from RPCA to EA, compared to 2% (1/49) from EA to RPCA ($P = 0.035$).

In the RPCA group 10% (5/49) developed a temperature ≥ 38 °C, compared to 37% (18/49) in the EA and 7% (3/42) in the control group ($P < 0.001$). The mean maternal temperature was lower in the remifentanil and control groups compared to the epidural group (Fig. 2). Intergroup comparison showed that the mean temperature after 2 and 4 h was significantly higher in the epidural group, although differences were small: EA: 37.3 ± 0.52 °C versus RPCA: 37.0 ± 0.54 °C and control: 37.0 ± 0.59 °C (2 h, $P = 0.02$) and EA: 37.6 ± 0.53 °C versus RPCA: 37.2 ± 0.43 °C and control: 37.0 ± 0.27 °C (4 h, $P = 0.01$). A post hoc test with Bonferroni correction for multiple comparisons comparing epidural to remifentanil and epidural to controls showed that parturients undergoing epidural analgesia had significantly higher temperature compared to remifentanil. (Table 2). Fever occurred in all cases during the first stage of labour (the dilation phase). Univariate analysis of determinants of maternal fever is shown in Table 3. Factors entered in the multivariate regression with backward selection were type of analgesia, maternal age, weight, parity, duration of first stage, duration of rupture of membranes, use of oxytocin and internal fetal monitoring. Multivariate analysis revealed that duration of the first stage of labour in combination with EA increased the probability of fever (Table 4). In the RPCA group 6% (3/49) of the parturients received antibiotic treatment versus 12% (6/49) in the EA and 5% (2/42) in the control group ($P = 0.345$; Table 1).

Significantly more women in the RPCA group experienced one or more periods of oxygen desaturation compared to the EA and control (Table 5). This was the case for SpO_2 values dropping ≤ 92% as well as $SpO_2 < 90\%$, for durations > 1 min and > 2 min (Table 5). Twenty percent (10/49) of the parturients on RPCA received oxygen compared to none in the epidural and control groups. Distribution of SpO_2 within groups is shown in Figure 3.

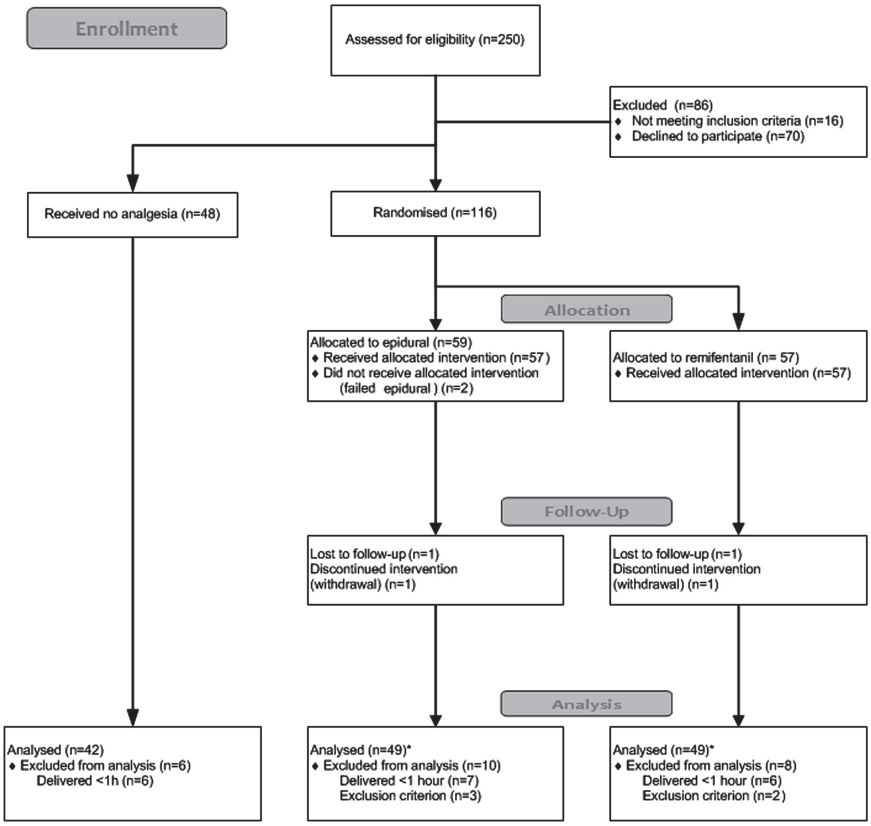

Figure 1. Study Flowchart. * Intention-to-treat analysis

Table 1. Maternal and labour characteristics

	Control (n=42)	EA (n=49)	RPCA (n=49)	p value C vs EA vs. RPCA
Age (yr)	33 (4.5)	31 (5.6)	32 (4.8)	0.36
Height (cm)	173 (5.1)	170 (7.6)	169 (6.9)	0.05
Weight (kg)	83 (13.3)	81 (12.6)	81 (17.2)	0.78
Primiparity (%)	11 (26)	27 (56)	25 (52)	0.01
Gestation (weeks)	40	40	39	0.17
Cervical dilation at randomisation (cm)	NA	4 (1.3)	4 (1.2)	0.65
Duration first stage of labour (min)	224 (131)	434 (158)	355 (179)	<0.001
Duration second stage of labour (min)	24 (24.1)	40 (28.9)	35 (29.9)	0.02
Duration of rupture of membranes	327 (237)	233 (213)	192 (298)	0.003
Oxytocin used (%)	64	88	77	0.03
Delivery (%)				0.14
Spontaneous	34 (81)	29 (60)	32 (67)	
Instrumental	3 (7)	9 (19)	9 (19)	
Caesarean	5 (12)*	10 (21)	7 (15)*	
Missing**		1	1	
Remifentanil administered (µg)			1417	
Duration of labour pain treatment	NA	234 (151)	192 (116)	
Crossover to RPCA/EA (%)	NA	1 (2)	8 (17)	
Use of antibiotics	2 (5)	6 (12)	3 (6)	0.35

Data are mean (SD), % or n.
C Control; EA Epidural Analgesia; RPCA Remifentanil.
* Pain relief during caesarean section: spinal anaesthesia
** Due to loss of identification

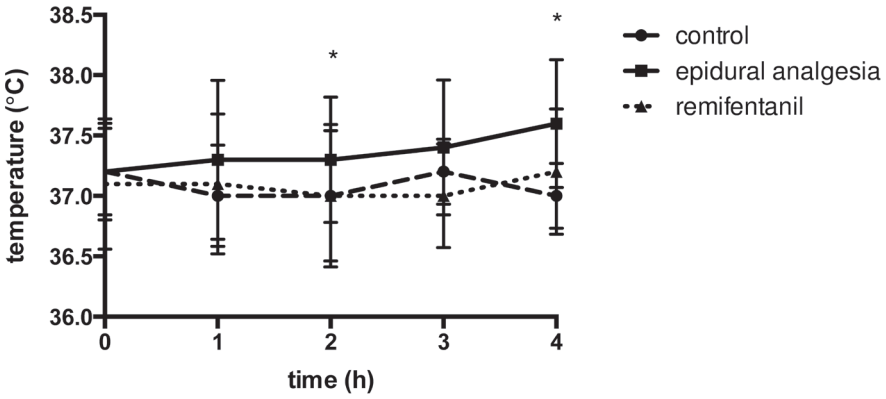

Figure 2. Mean temperature as a function of time for remifentanil, epidural analgesia and control group. Vertical bars represent SD. * P < 0.05

Table 2. Mean maternal temperature

Mean Temperature	Control (*n*=42)	EA (*n*=49)	RPCA (*n*=49)	*p* value C vs EA vs. RPCA	*p* value* EA vs. RPCA	*p* value* EA vs. C
Pre-analgesia	37.1 (0.36)	37.2 (0.40)	37.1 (0.54)	0.56	0.49	1.00
1h	37.0 (0.42)	37.3 (0.66)	37.1 (0.58)	0.09	0.13	0.12
2h	37.0 (0.59)	37.3 (0.52)	37.0 (0.54)	0.02	0.04	0.18
3h	37.2 (0.27)	37.4 (0.56)	37.0 (0.43)	0.10	0.003	0.65
4h	37.0 (0.27)	37.6 (0.53)	37.2 (0.52)	0.01	0.04	0.11

Data are mean (SD).
C Control; EA Epidural Analgesia; RPCA Remifentanil.
*Post hoc analysis (ANOVA) with Bonferroni correction for multiple comparisons

Table 3. Univariable analysis of determinants of maternal fever (t ≥ 38.0 °C)

Factors	OR	CI	*p* value
Type of analgesia			
Epidural analgesia**	4.75	1.44-15.6	0.01
Remifentanil**	1.11	0.28-4.41	0.89
Age	1.05	0.96-1.15	0.31
Weight	1.03	1.00-1.06	0.09
Parity	0.64	0.35-1.16	0.14
Nulliparity	2.03	0.84-4.91	0.12
Internal fetal monitoring			0.21
Scalp electrode	1.38	0.41-4.65	0.60
Intra uterine pressure recording	1.81	0.16-20.5	0.63
Both	3.63	0.94-13.9	0.06
Use of oxytocine	4.2	0.95-18.9	0.06
Duration of first stage of labour	1.01	1.00-1.01	0.001
Duration of second stage of labour	0.01	0.99-1.03	0.37
Duration of rupture of membranes	1.00	1.00-1.01	0.003

OR Odds Ratio; CI Confidence Interval
** compared to control

Table 4. Multivariable analysis of determinants of maternal fever

Factors	OR	CI	*p* value
Type of analgesia			0.02
Epidural analgesia*	7.44	0.80-68.8	0.08
Remifentanil *	0.93	0.07-12.5	0.96
Duration of first stage of labour	1.01	1.00-1.01	0.01

* compared to control

One serious adverse event occurred in the RPCA group. In this particular case, administration of remifentanil was stopped after 65 min because of low respiratory rate (average 5/min) and low maternal SpO_2 (lowest 71%) despite the administration of supplemental oxygen. A total of 660 µg remifentanil had been administered. After the event pump setting, the syringe and remifentanil ampoules were checked. No abnormalities were found. Maternal SpO_2 and respiratory rates rapidly recovered, without further intervention.

Table 5. Maternal saturation and sedation scores

	Control (n=39)	Epidural (n=34)	Remifentanil (n=40)	*p* value C vs EA vs. RPCA
Saturation – duration				
<92% - 1 min	9 (23)	10 (29)	27 (68)	<0.001
<92% - 2 min	6 (15)	4 (12)	15 (38)	0.01
<92% - 5 min	0	2 (6)	3 (8)	0.24
<90% - 1 min	8 (20)	5 (15)	19 (48)	0.003
<90% - 2 min	4 (10)	3 (9)	12 (30)	0.02
<90% - 5 min	0	1 (3)	1 (3)	0.58
Sedation scores	**(n=42)**	**(n=49)**	**(n=49)**	
Pre-analgesia	1.1 (0.26)	1.0 (0.20)	1.1 (0.25)	0.82
1 h	1.1 (0.22)	1.2 (0.44)	1.7 (0.64)	<0.001
2 h	1.0 (0.20)	1.2 (0.46)	1.7 (0.60)	<0.001
3 h	1.1 (0.42)	1.2 (0.41)	1.9 (0.73)	0.001
4 h	1.2 (0.45)	1.1 (0.35)	1.8 (0.62)	0.01

Data are n (%). C Control; EA Epidural Analgesia; RPCA Remifentanil.

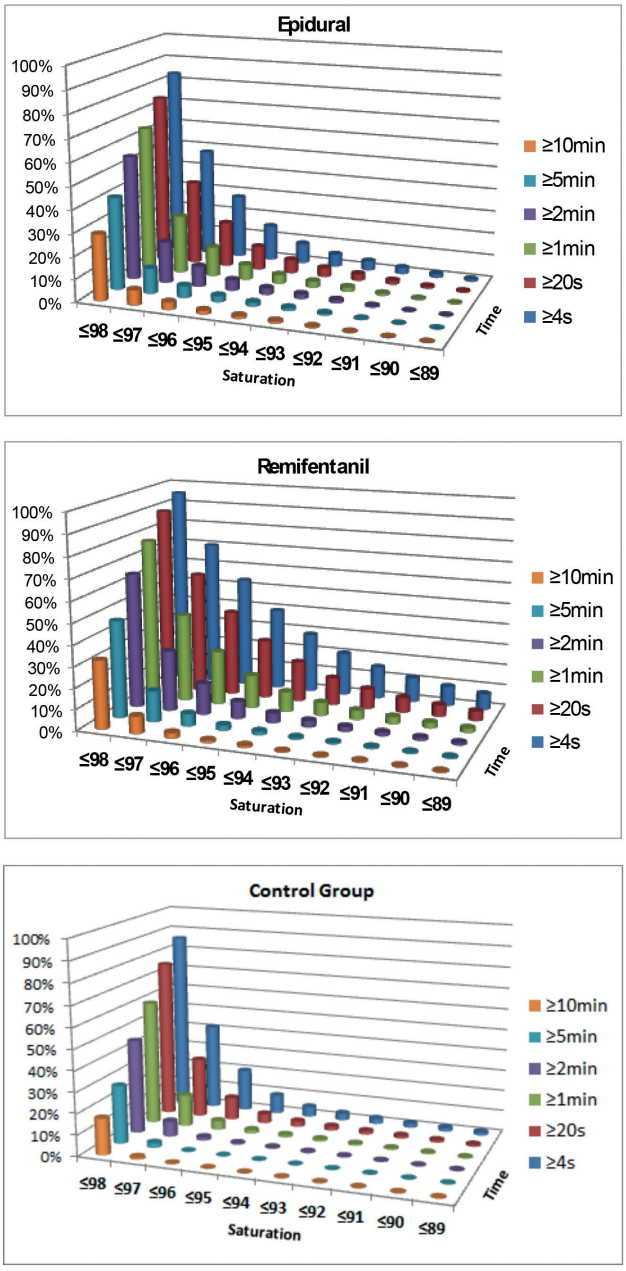

Figure 3. Distribution of SpO_2. x axis represents minimum duration of episode, y axis represents minimum saturation levels, z axis represents percentage of the total time.

Prior to treatment VAS pain scores were similar in RPCA and EA groups (8.3 ± 1.3 versus 7.8 ± 1.4 cm). Treatment reduced VAS scores in both groups at t = 1 h, with significantly lower scores in EA group compared to the RPCA group. At 2 h of treatment the difference in VAS scores became even more apparent with increasing scores in parturients receiving RPCA while low scores persisted in patients on EA. This difference persisted through the study period (Fig. 4). Pain scores in the control group were lower upon arrival in the delivery room (5.4 ± 2.8 cm) compared to the measurement before analgesia in the two treatment groups but increased and were greater than values observed in the two treatment groups from t = 1 h until the end of the study period. Overall satisfaction, scored after delivery, was similar in all groups (RPCA: 8.1 ± 1.2, EA: 8.4 ± 1.2, control: 8.0 ± 1.0, p = 0.253).

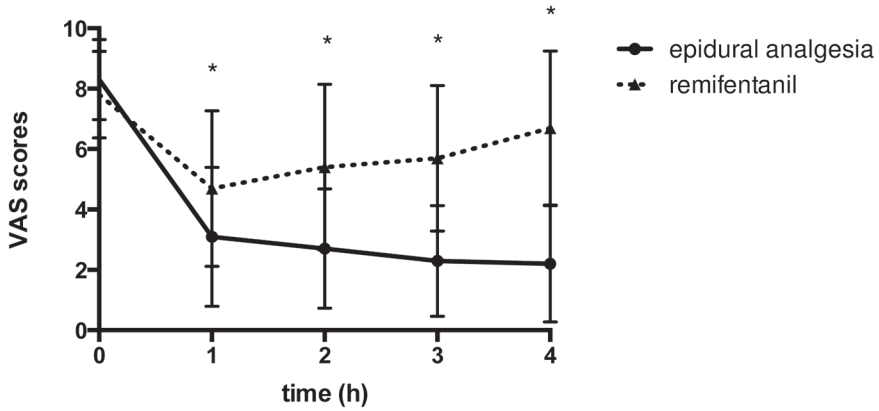

Figure 4. Mean VAS pain scores as a function of time for remifentanil and epidural analgesia. Vertical bars represent SD. * P < 0.05

The incidence of nausea was higher in the RPCA group compared to the EA and control groups (RPCA: 59% (29/49) versus EA: 39% (19/49) versus control: 36% (15/42), $P = 0.037$), as well as the incidence of vomiting (RPCA: 53% (26/49) versus EA: 22% (11/49) versus control: 12% (5/42), $P < 0.001$). Comparing RPCA to EA, differences were statistically significant. Sedation scores were significantly higher in the RPCA (maximum score 1.9 ± 0.4) group than in the EA (1.2 ± 0.7) group; the maximum score in the control group was 1.2 ± 0.4 ($P < 0.005$, Table 5). Itching was comparable in the RPCA and EA groups (RPCA: 18% (9/49) versus EA: 16% (8/49); in the control group no itching was reported (p=0.014).

Haemodynamic variables (blood pressure and HR) remained within normal range in all groups. One hour after pain medication started, maternal HR was significantly lowest in the remifentanil group (RPCA: 77 ± 11 beats/min, EA: 83 ± 13 beats/min,control: 83 ±12 beats/min, $P = 0.027$). Thereafter, no statistically significant HR differences were detected.

Mean Apgar scores, fetal cord blood and fetal heart traces were within normal range and similar among treatments (Table 6). However in 4 cases umbilical cord pH was below 7.10 in the EA group (range 7.04 to 7.07). In three of these cases fetal distress was apparent on the cardiotocogram, which led to intervention: two neonates were born after ventouse extraction (Apgar scores 7/9 and 6/9); one neonate was born after Caesarean section (Apgar 8/9). In one baby, a low umbilical pH became apparent after a normal spontaneous birth (Apgar 9/10). None of these babies had fever; three mothers, however, did have fever (range 38.0-38.6 °C).

Four neonates in the EA group and 3 in the RPCA group were treated for possible sepsis. All blood cultures turned out negative. In the control group two neonates were treated with antibiotics, one of which had a positive blood culture (group B streptococcus).

Table 6. Fetal and neonatal characteristics

	Control (n=42)	Epidural (n=49)	Remifentanil (n=49)	*p* value C vs EA vs. RPCA
Apgar score 1 min	8.7 (0.77)	8.3 (1.48)	8.6 (1.12)	0.71
Apgar score 5 min	9.7 (0.64)	9.5 (0.66)	9.5 (1.18)	0.33
Apgar score < 7 at 5 min	0	0	2	0.13
Cord blood pH	7.25 (0.08)	7.21 (0.09)	7.23 (0.07)	0.08
Cord blood BE	-5.0 (3.26)	-6.6 (2.86)	-5.6 (3.06)	0.05
pH < 7.10	0	4	0	0.02
CTG reactive (%)	35 (83)	40 (89)	44 (94)	0.31
Neonatal fever	2	2	2	0.99
Sepsis work-up	2	4	3	0.68
Positive blood culture	1	0	0	0.39

Data are mean (SD) and (%). C Control; EA Epidural Analgesia; RPCA Remifentanil. CTG Cardiotocogram; BE Base Excess.

DISCUSSION

Our study showed that the incidence of hyperthermia and fever was greater in women receiving EA for labour pain compared to women who received RPCA, while the incidence of hypoxaemic events was greater in women on RPCA.

In our study 37% of the parturients on EA developed fever, a known side effect of EA.[2 4 15] This incidence is substantially higher compared to other studies. For example, Philip et al.[2] and Evron et al.[15] found that 15% and 14% of women on EA developed a fever, respectively. We observed that the incidence of fever was comparable between RPCA (10%) and control (7%) patients. Our data therefore do not support the theory that opioids suppress hyperthermia during labour and delivery. We relate the higher occurrence of fever in the EA groups to an EA-dependent impairment of thermoregulatory control occurring in some women. Further studies are required to assess the apparent selectivity of this effect.

Episodes of hypoxaemia were more frequent and lasted longer in patients on RPCA compared to EA or no analgesia. Moreover, mean saturation scores were significantly lower with RPCA. These results are in agreement with previous observations and demonstrate a higher risk for respiratory depression during RPCA.[6, 9, 11, 16-19] Although we did not observe any episodes of apnoea, the observation of longer and deeper hypoxic events is worrisome as this may have yet unknown future effects on the neonate and may lead to maternal cardiorespiratory collapse. Indeed, severe adverse cardiorespiratory effects of remifentanil have been described.[20-24] In our study one adverse event occurred. In this patient administration of remifentanil was discontinued because of persistent SpO_2 levels of 70 to 80% combined with a RR < 8/min. One additional observation made in our study is of importance. Even under strict surveillance, a rather large proportion of low saturation values remained unnoticed since only 20% of the parturients received additional oxygen. We further hypothesise that the greater sedation levels during RPCA may have contributed significantly to the occurrence of respiratory depression independent of the direct effect of the opioid on the ventilatory control system.

In agreement with previous studies, EA provided better analgesia compared to RPCA.[6,9,15] Following RPCA, pain scores increased after 1-h and returned towards baseline. This is possibly related to the development of tolerance to remifentanil. Irrespective of treatment, satisfaction scores were similar, again consistent with earlier studies comparing RPCA and EA.[9, 16]

Neonatal outcome was acceptable in all treatment groups. We have no explanation for

the occurrence of low umbilical arterial pH (< 7.10) in four neonates of mothers treated with EA, as EA is not associated with poor neonatal oucome.[4, 25] We relate the fetal distress to maternal factors rather than to the mode of analgesic treatment.

In case of maternal fever during labour in women treated with EA it is difficult to discriminate between a maternal infection and an increase of temperature by EA. As a result, neonates of mothers with fever are more likely to be admitted and treated for possible sepsis. Because all blood cultures in the epidural group turned out negative, there is no indication that the increase in temperature during administration of EA is related to neonatal infection.

Our study design has several limitations. (1) Randomisation was limited to parturients requesting analgesia; we included parturients that did not request any analgesia into the control group. We felt that it was impractical and unethical to randomise parturients at the time of inclusion into three treatment groups. If we had randomised parturients into three groups we expected that many of the parturients in the control group would ultimately request analgesia and drop out of the study. Similarly, the analgesic groups would have a number of parturients that would drop out because they would not request analgesia. The use of a separate control group made alignment of the data difficult. We believe however that our approach leads to a valid and clinically relevant comparison. (2) The study was not blinded. This could have had some effect on pain and sedation scores. However we do not believe that our open study affected temperature data, the main end-point of our study. (3) Although attending obstetricians act on their own account regarding antibiotic use, most do treat a suspected intrauterine infection with maternal antibiotic therapy. We do not believe that the absence of specific guidelines for antibiotic therapy affected our outcome significantly. (4) We performed an intention-to-treat-analysis. Crossover occurred in just 9 of 140 women. While data acquisition was intended to continue, in many cases this was not the case. Hence, we did not perform a *per protocol* analysis. Taken the low number of crossovers we argue that our approach did not affect the validity of the study outcome.

In conclusion, we observed that EA was associated with a greater incidence of fever, while RPCA caused more and deeper hypoxaemic events and more sedation and nausea. These results confirm the concerns about respiratory depression during administration of remifentanil and emphasise the need for continuous monitoring by trained staff.

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Chapter 5

High inspired oxygen concentration increases the speed of onset of remifentanil-induced respiratory depression

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We previously showed in 20 healthy volunteers that respiratory depression from remifentanil is more pronounced during inspiration of a high oxygen concentration (50% oxygen in nitrogen) than during inspiration of room air as determined from minute ventilation, end-tidal carbon dioxide concentration and respiratory rate.[1] The descriptive analysis of the data indicated that a bolus dose of 50 µg remifentanil caused a depression of ventilation from 7.4 (1.3) (mean (SD)) to 2.2 (1.2) L/min and during hyperoxia from 7.9 (1.0) to 1.2 (1.2) L/min ($P < 0.01$). We hypothesized that the additional respiratory depressant effect during hypoxia was related to a reduced drive from the carotid bodies during exposure to hyperoxia, causing an apparently greater potency of the opioid in causing respiratory depression.

We here present the results of a pharmacokinetic pharmacodynamic analysis of the data of our previous study[1] to further understand the mechanism through which oxygen interacts with remifentanil on ventilation. A population pharmacokinetic pharmacodynamic (PKPD) analysis on the ventilation data was performed in NONMEM (software for nonlinear mixed effects modeling; ICON Development Solutions, Hanover, MD, United States).[2] Since no blood samples were obtained for the determination of the remifentanil plasma concentration, we simulated the pharmacokinetic data using the 3-compartment PK data set of Minto et al.[3] Ventilation (Ve) was described by a sigmoid EMAX model of the form: $Ve(t) = V_0/[1 + (Ce(t)/C50)^y]$, where V_0 is baseline ventilation, Ce the remifentanil effect-site concentration, C50 the remifentanil concentration causing 50% reduction in ventilation and y a shape factor. To eliminate a possible delay between the remifentanil plasma concentration and effect, an effect compartment was postulated with blood-effect-site equilibration half-life $t_{1/2}ke0$. All data were simultaneously analyzed with the inspiratory oxygen concentration as covariate. Significance of covariates was tested by X^2 test with P-values < 0.01 considered significant.

Examples of pharmacodynamic data fits of three 'typical' subjects are given in Figure 1A-C. Remifentanil induced a rapid reduction in ventilation that was more pronounced during the inhalation of 50% oxygen (Fig. 1C) than during air breathing (Fig. 1A and B). Inspection of the individual data fits indicates that the PKPD model adequately described the data (orange lines in Fig. 1). Typical parameter estimates (SE) V_0 7.7 (0.2) (w^2 (variance) 0.02 (0.005)), C50 2.6 (0.2) ng/mL (w^2 0.10 (0.02)), y 2.0 (0.2) (w^2 0.08 (0.03)). Parameter $t_{1/2}ke0$ was the only parameter that depended on the inspired oxygen concentration ($P < 0.01$) with a typical value during the inhalation of 21% oxygen of 1.60 (0.26) min and 50% oxygen of 0.59 (0.19) min (w^2 for both 0.58 (0.24)).

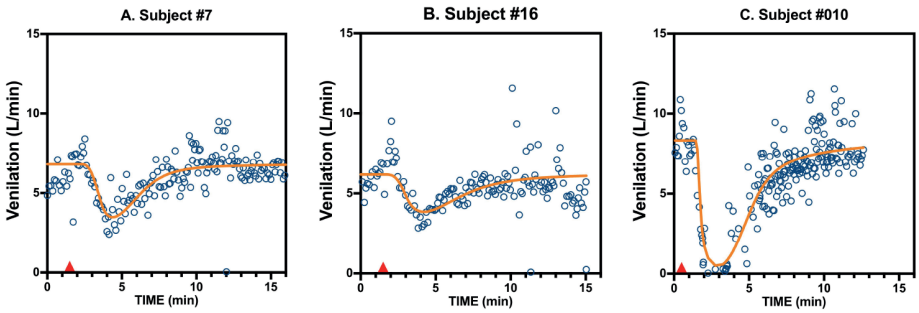

Figure 1. Examples of data fits of the effect of remifentanil on breathing obtained in three volunteers. Each blue circle is one breath; the orange lines are the predicted ventilations; the red trangle is the remifentanil bolus administration (50 µg). A and B are data sets obtained during air breathing. C during breathing of high-inspired oxygen.

We previously speculated that the greater respiratory effect of remifentanil during the inhalation of supplemental oxygen was related to the loss of the carotid body function under hyperoxemic conditions, losing about 30% of ventilatory drive and consequently making remifentanil more potent than under conditions of ambient air breathing.[1] The current analysis shows no change in remifentanil potency (C50) between breathing 21% or 50% oxygen. However, we now show that high inspired oxygen increases the speed of onset/offset of remifentanil causing deeper nadirs in ventilation following a single short infusion of 50 µg. The mechanism through which oxygen affects $t_{1/2}ke0$ remains unknown at present. Parameter $t_{1/2}ke0$, the link parameter between PK and PD, is determined by the transport of the drug from arterial blood to the brain, passage across the blood-brain-barrier, equilibration within the brain compartments, receptor kinetics, and translation of receptor activation into effect. Possibly, the speeding up of the response to remifentanil by oxygen may be related to hypercapnia-induced cerebral vasodilation (with brain hypercapnia related to the reduction of the Haldane effect), causing a more rapid equilibrium between plasma and brain remifentanil concentrations. Evidently, further studies are needed to further understand the complex interaction between oxygen and opioids on breathing.

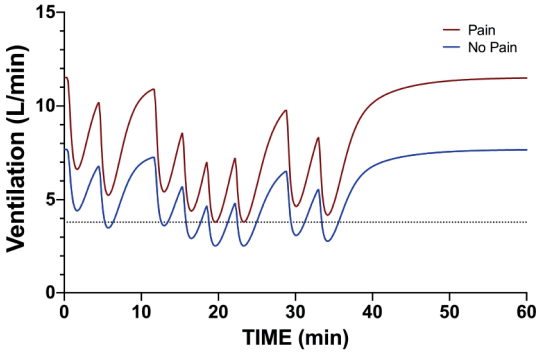

Figure 2. Simulation of the effect of multiple remifentanil bolus administrations (30 µg) on ventilation during conditions of no pain (blue) and under conditions of constant mild to moderate pain (red), causing an increase in baseline ventilation by about 50%.

Additionally, the results of both analyses may be used to predict ventilation under various circumstances, such as the during the use of PCA remifentanil for pain (or sedation). One such analysis is given in Fig. 2.

Here the effect of PCA remifentanil administration (bolus dose of 30 ug at irregular intervals) is simulated on ventilation under conditions of no pain (blue line) and pain (red line). The horizontal dotted line depicts 50% ventilatory depression observed under no pain conditions. One indication of remifentanil PCA is labor pain.[4] Clearly this simulation (derived from data obtained in healthy non-pregnant population) can not directly be extrapolated to women in labor pain. In pregnancy, the ventilatory control system is affected by multiple factors not addressed here such as alterations in body weight, FRC, hormonal status, and the frequent occurrence of sleep-disordered breathing (which may later carotid body sensitivity). Still our analysis is the first attempt to describe the significant changes in ventilation during PCA remifentanil. Prospective studies in labor pain as well as under other circumstances are needed to further address and understand the effects of potent opioids on breathing in vulnerable populations.
In conclusion, we showed that high-inspired oxygen affects the blood-effects-site equilibration half-life ($t_{1/2}ke0$) of remifentanil, speeding up its onset and offset of effect on respiration and consequently causing deeper falls in ventilation.

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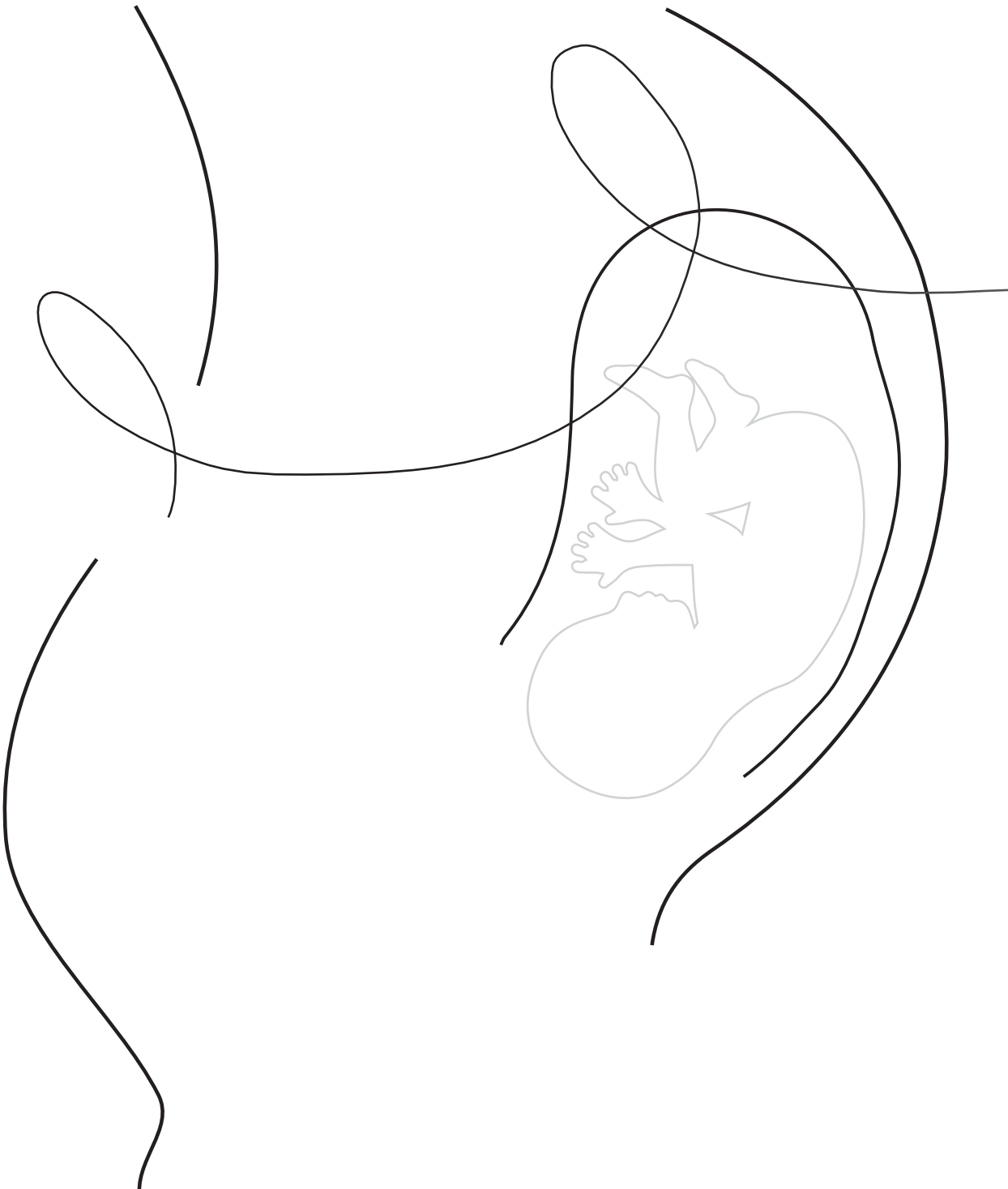

Chapter 6

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

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Submitted

INTRODUCTION

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

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

METHODS

Search Strategy

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

Inclusion and Exclusion Criteria

All randomised controlled trials and observational studies that compared efficacy and side effects of remifentanil with any other labour analgesic modality were included. Studies that were considered had to contain clinical data on maternal side effects (e.g., respiratory depression, hypotension, nausea, pruritus, sedation) and a clear description of how these data were collected. The full text article had to be available and only articles written in English language were included. Two authors (MD, LF) retrieved eligible articles and excluded irrelevant trials. Any discrepancies during data extraction were resolved by consulting a third author (AD). We choose not to restrict our analyses to randomised controlled trials but also to include observational studies as our aim was to review side effects of remifentanil and observational studies are suitable for the review of such data.

Outcome Measures

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

Validity assessment

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

Statistical analysis

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

RESULTS

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

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

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

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

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

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

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

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

Tveit et al.[13]	2012	Remifentanil PCA	17	Bolus 0.15 μg kg^{-1}, increasing dose steps 0.15 μg kg^{-1}, no max; lockout 2 min	No	3,4,5,6,7,8,9,10,11,12,13
		Epidural analgesia	20	Loading dose 15 mL ropivacaine 1mg mL^{-1} with fentanyl 2 μg mL^{-1}, continuous infusion		
Stocki et al.[12]	2013	Remifentanil PCA	19	Bolus 20-60 μg; lockout 2 min	No	1,3,4,5,7,8,9,12
		Epidural PCA	20	Loading dose 15 mL 0.1% bupivacaine with 50 μg fentanyl followed by PCA infusion of 0.1% bupivacaine with 2 mcg mL^{-1} fentanyl: basal infusion 5 mL h^{-1}, PCA bolus 2 mcg mL^{-1}; lockout 20 min		
	2015	Remifentanil PCA	49	Bolus 40 μg; lockout 2 min	No	1,2,3,4,5,6,7,8,9,1011,12,13
		Epidural analgesia	49	Loading dose 12.5 mL 0.2% ropivacaine ropivacaine 0.1% with sufentanil 0.5 μg mL^{-1} continuous infusion		
Freeman et al.[23]	2015	Remifentanil PCA	687	Bolus 20-40 μg; lockout 3 min	No	1,3,5,6,7,8,9,10,11,12,13
		Epidural analgesia	671	Local protocol		
Ismail et al.[24]	2011	Remifentanil PCA	380	Bolus 0.1-0.9 μg kg^{-1}; lockout 1 min	No	5,7,8,12,13
		Epidural analgesia	380	Loading dose 8 ml 0.125% levobupivacaine with fentanyl 2 μg mL^{-1} continuous infusion		
Volmanen et al.[21]	2005	Remifentanil PCA	15	Bolus 0.4 μg kg^{-1}; lockout 1 min	No	1,3,4,5,7,10
		Nitrous oxide	15	Local protocol		
Lin et al.[25]*	2014	Remifentanil PCA	170	Bolus 0.4 μg kg^{-1}; lockout 5 min Background infusion 0.04-0.05 μg kg^{-1} min^{-1}	Yes	2,3,4,5,7,8,10,11
		Epidural PCA	200	Loading dose 10 mL 0.068% ropivacaine with sufentanil 0.3 μg ml^{-1} followed by maintenance dose at 8 mL h^{-1}, PCA bolus 5 mL; lockout 15 min		
Marwah et al.[26]*	2011	Remifentanil PCA	47	Bolus 0.25 μg kg^{-1}; lockout 2 min Background infusion 0.025-0.05 μg kg^{-1} min^{-1}	Yes	1,2,4,5,6,7,8,9,12,13
		Fentanyl PCA	51	Bolus 25-50 μg; lockout 3 to 6 min	No	

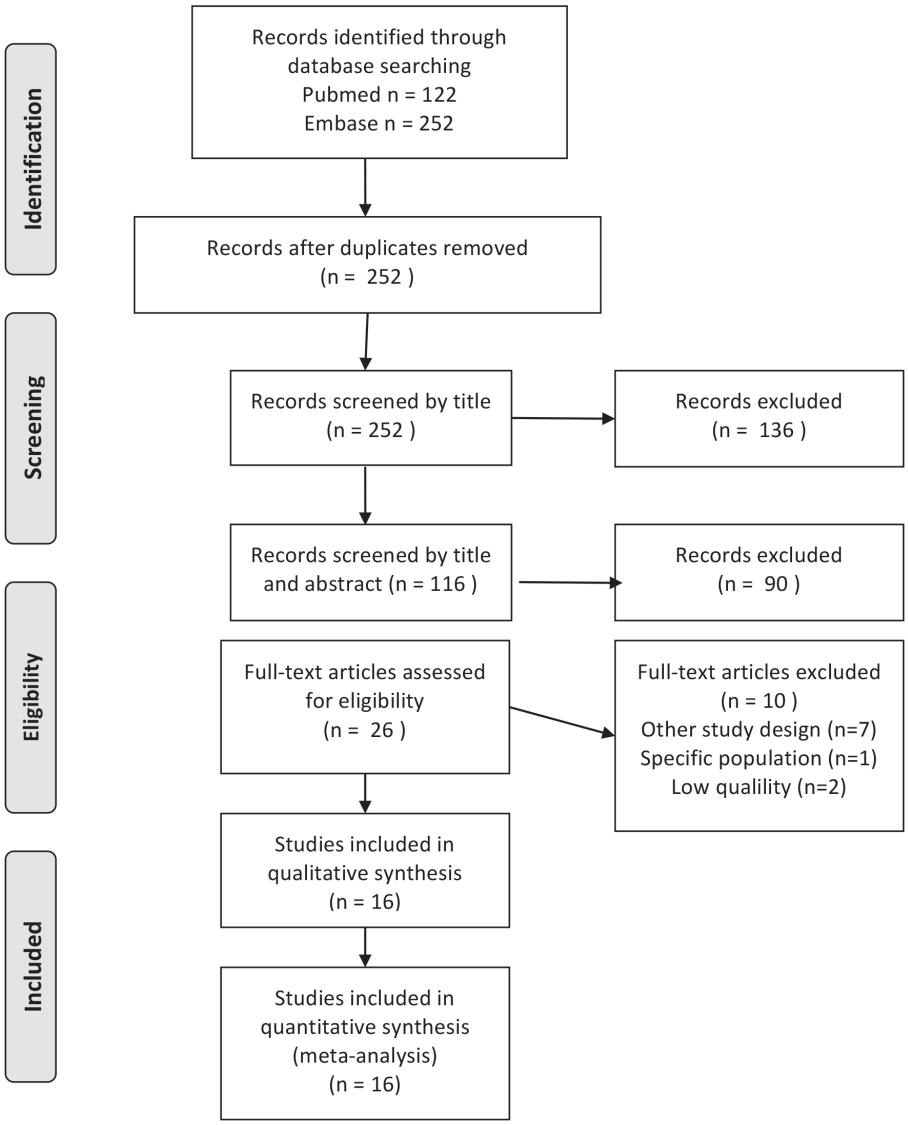

Figure 1. Study flow diagram.

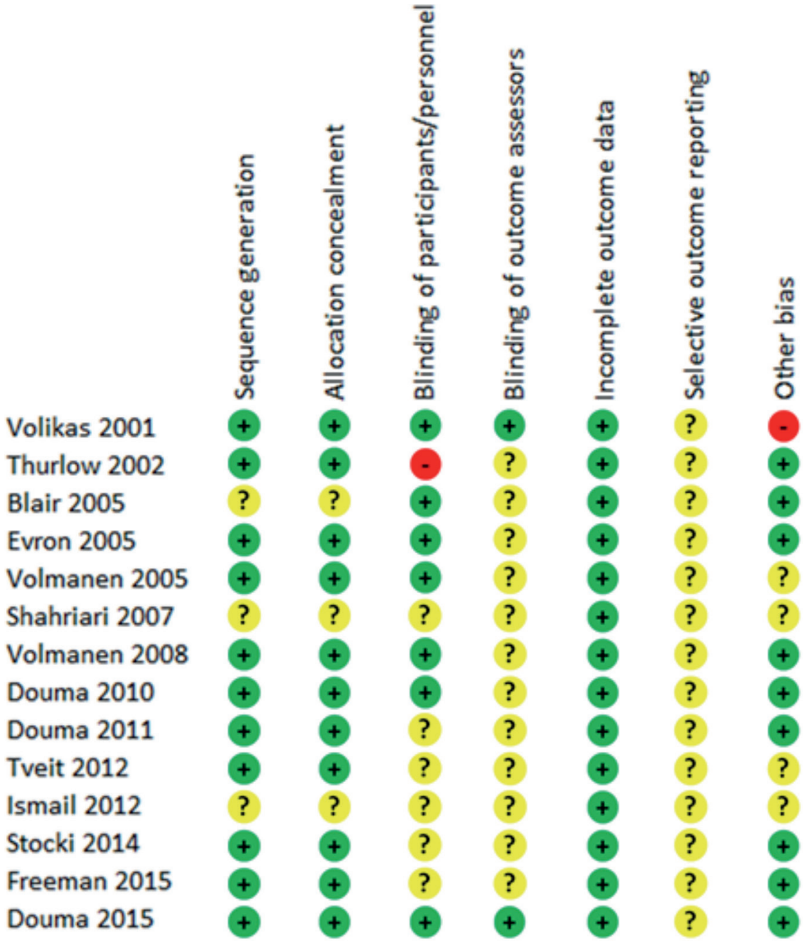

Figure 2. Risk of bias assessment.

Primary outcome

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

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

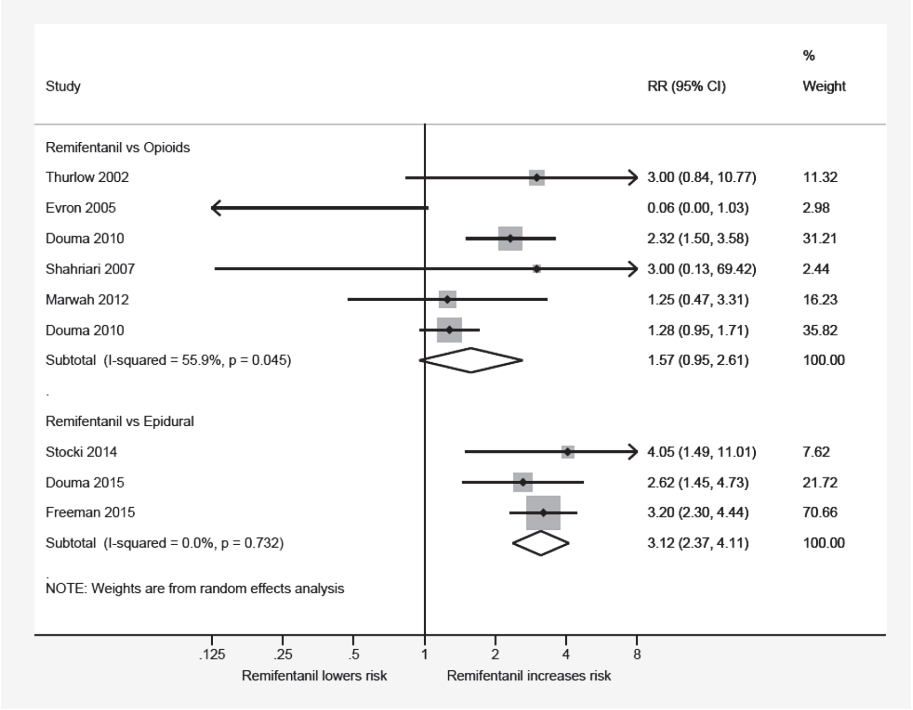

Figure 3. Number of parturients with oxygen desaturation < 95% in women receiving remifentanil versus other labour analgesics.

Secondary outcomes

Maternal desaturation below 90%. Only three trials, involving 566 women, investigated the incidence of SpO_2 < 90%, therefore we were not able to pool data. In one retrospective study RPCA (47 women) was compared to fentanyl PCA (51 women). No difference was found in SpO_2 < 90% between RPCA and fentanyl (RR 4.70, 95% CI 0.83-26.53).[26] Two trials comparing RPCA to EA reported the incidence of SpO_2 < 90%. One trial reported zero parturients with SpO_2 < 90%, irrespective of treatment.[25] In contrast, Douma et al. described that women on RPCA had a significantly increased risk for desaturations below 90% compared to EA (19/40 vs 5/34, RR 3.02 95% CI 1.32–6.93).[20] One serious adverse event was reported in this study with oxygen saturation of 71% in combination with low respiratory rates (average 5 breaths min^{-1}).

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

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

Nausea (Fig. 4). The risk of developing nausea was similar in patients receiving remifentanil to any of the other opioids (4 trials; RPCA 160, other opioids 221 women; RR 0.89, 95% CI 0.66-1.21).[3, 5, 7, 26] In contrast, patients on RPCA had a higher risk of

developing nausea compared to EA (8 trials; RPCA 1112; EA 1045 women; RR 1.56, 95% CI 1.25-1.95; Fig 4).[10-13, 20, 23-25] No significant difference was detected in the N_2O study (RR 1.18 95% CI 0.48-2.88).[21]

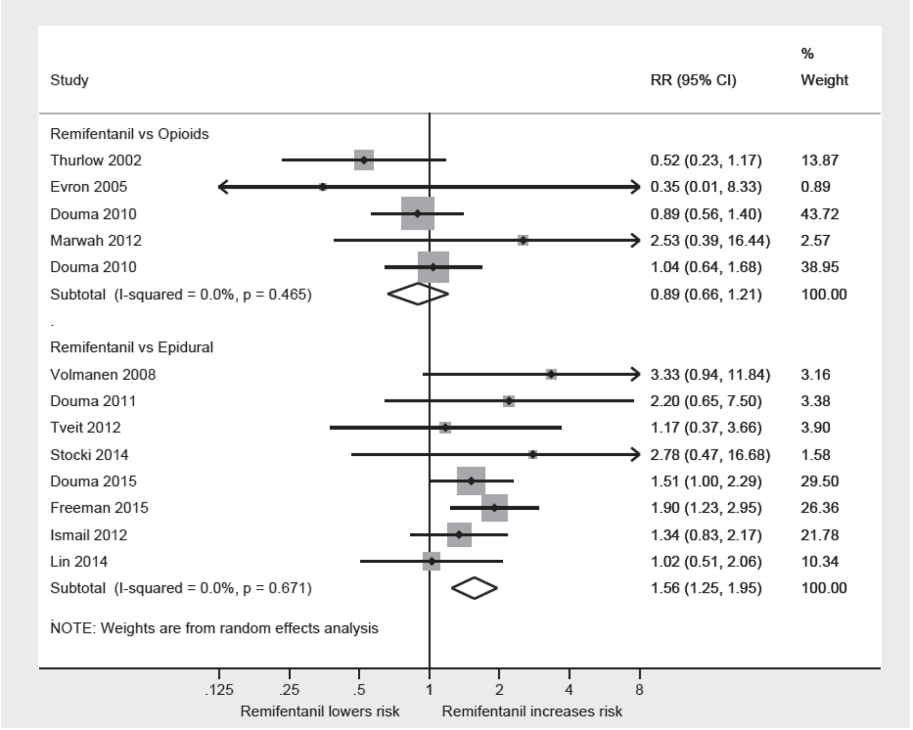

Figure 4. Number of parturients developing nausea/vomiting during remifentanil versus other labour analgesics.

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

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

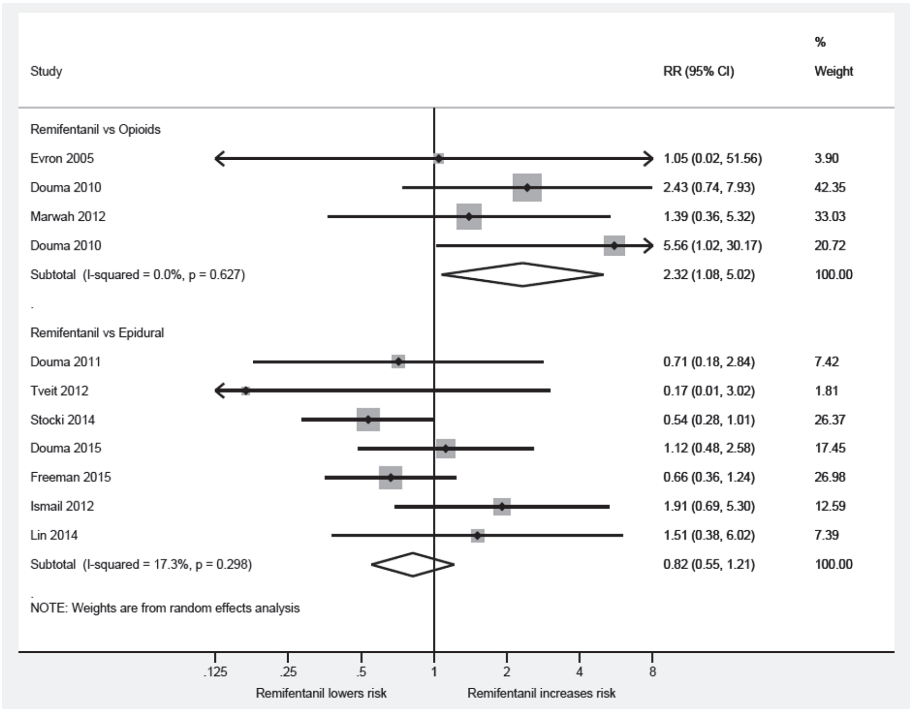

Figure 5. Pruritus in parturients receiving remifentanil versus other labour analgesics.

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

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

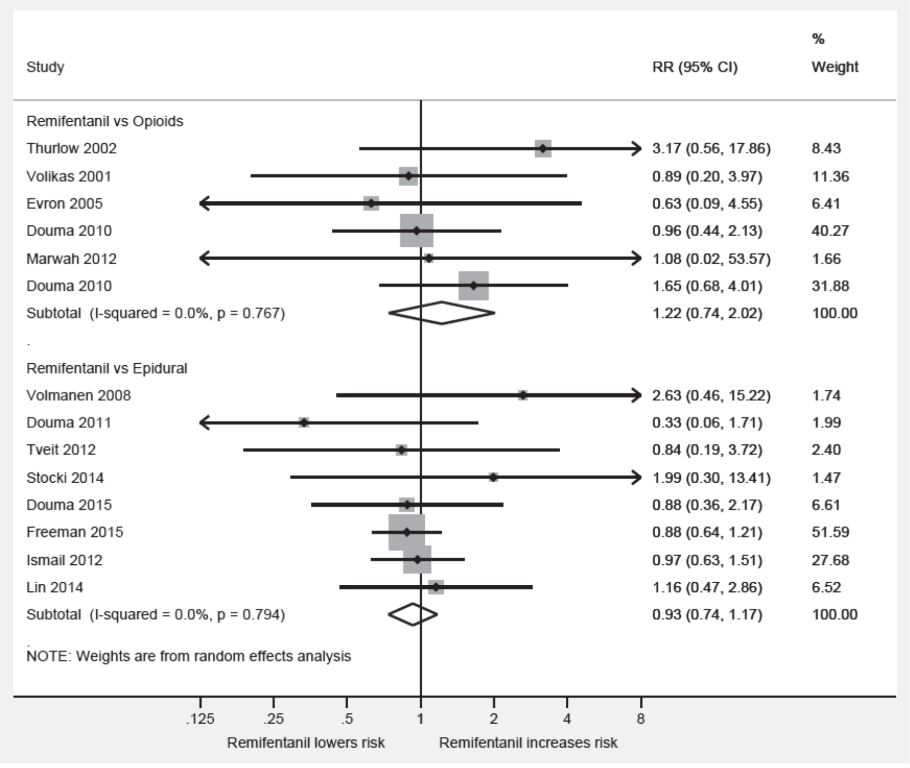

Figure 6. Instrumental delivery in parturients receiving remifentanil versus other labour analgesics.

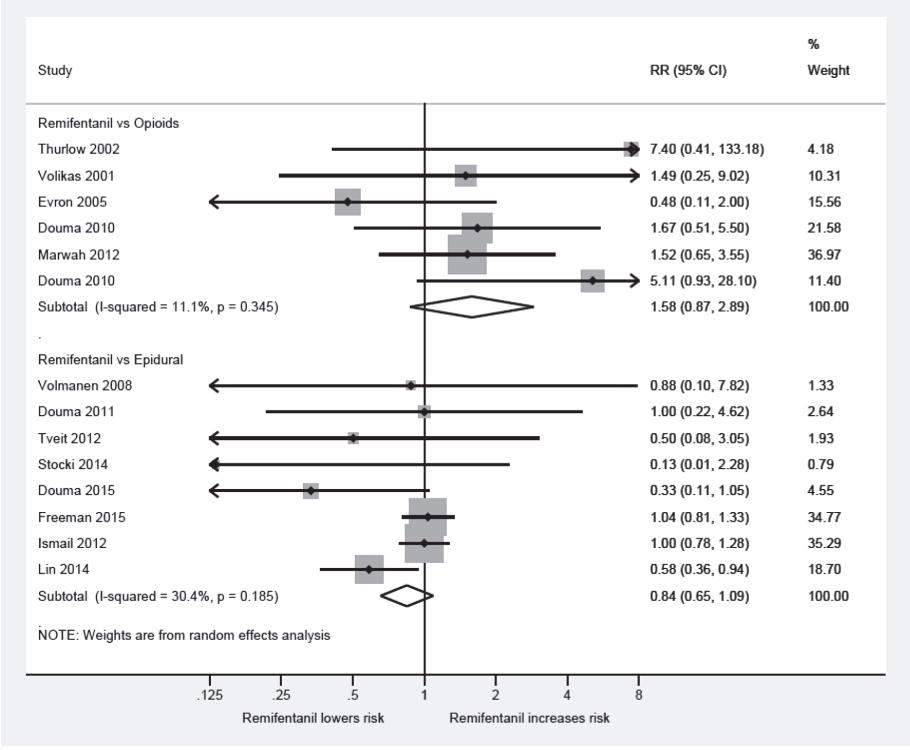

Figure 7. Caesearean section in parturients receiving remifentanil versus other labour analgesics.

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

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

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

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

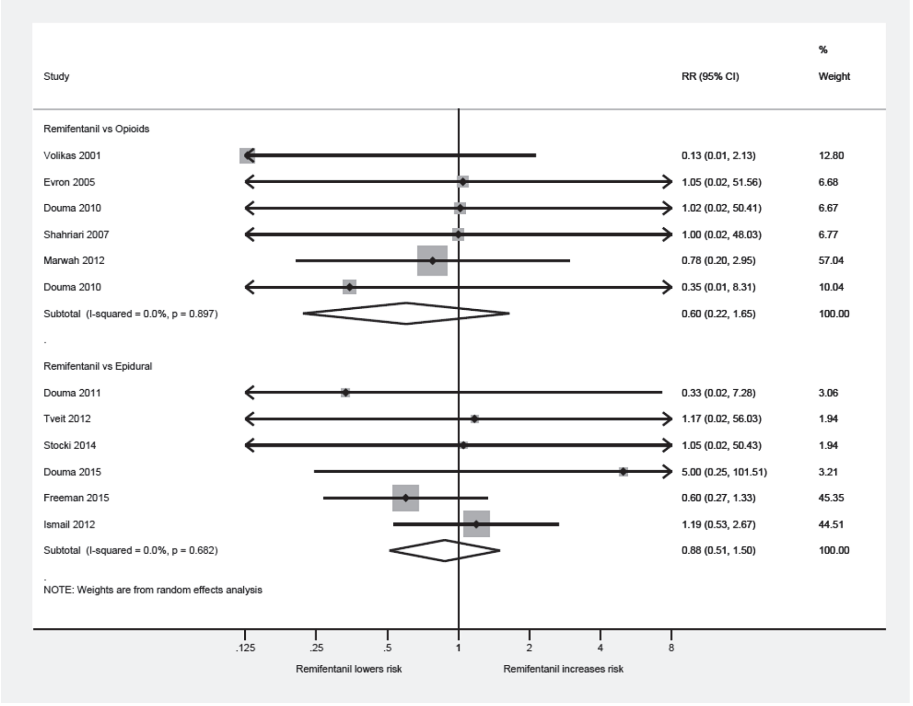

Figure 8. Number of Apgar scores <7 in neonates of which mothers received remifentanil versus other labour analgesics.

DISCUSSION

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

In terms of risk of a caesarean section no significant difference was observed among treatments. This is in agreement with previous systematic reviews comparing various methods of pain relief during labour.[31, 32] Interestingly, the need for instrumental delivery was not significantly different among treatments. This stands in contrast to the results of a systematic review from 2012, comparing EA against non-EA methods, which showed that women using EA were at increased risk of an instrumental delivery.[31] Our systematic review did not show any significant differences regarding to fetal heart rate traces or neonatal scores including Apgar scores and umbilical pH. None of the included trials described any neonatal adverse outcomes caused by remifentanil.

Limitations

There are some limitations to our review. First, there is substantial heterogeneity between studies with respect to various dose regimens, different pump settings and different comparative drugs regimens. In some studies patient-controlled systems

were compared to non-patient controlled (intramuscular or intravenous injections). Moreover, several studies allowed the use of N_2O (Entonox), which may have affected results. Secondly, included studies are relatively small and are mainly efficacy trials, not powered for a risk analysis of side effects. Different to previous systematic reviews, we have also included observational studies, given the fact that these studies can be an important source of data for adverse effects.[33] A final consideration is the fact that different cut-off points for outcome measurements were taken; for example the duration of oxygen desaturation. The cut-off point for oxygen desaturation ranged from 20 seconds to 60 seconds in various studies. Moreover, some of the studies did not mention the cut-off point. These limitations have to be taken into account while interpreting the results from this review.

Conclusions

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

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

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Chapter 7

Summary, future perspectives and conclusions

SUMMARY, FUTURE PERSPECTIVES AND CONCLUSIONS

The aim of this thesis was to evaluate the efficacy and safety of remifentanil in its treatment of labour pain.

Chapter 2 describes the comparison of the analgesic efficacy of remifentanil compared to pethidine (meperidine) and fentanyl during labour. One hundred fifty-nine parturients were randomly assigned to receive intravenous remifentanil, pethidine or fentanyl, in a patient controlled setting (PCA). Results showed a mild to moderate effect on pain relief (average pain scores remaining above 4.5 in all groups). During the first hour of treatment, remifentanil performed slightly better compared to pethidine and fentanyl, no differences existed thereafter. In all groups, pain scores returned to pre-treatment values within three hours after initiation of treatment, therefore the effect seemed to be time-limited. Remifentanil was associated with significantly more periods of maternal oxygen saturation < 95%, more sedation and more itching. No difference was seen in neonatal outcome. To conclude, the efficacy of pethidine, fentanyl, and remifentanil PCA for labour analgesia varied from mild to moderate. Remifentanil PCA provided better analgesia than pethidine and fentanyl PCA, but only during the first hour of treatment. In all groups, pain scores returned to pre-treatment values within 3 h after the initiation of treatment.

Epidural analgesia is considered the 'gold standard' in the area of obstetric analgesia. In chapter 3 we compared the efficacy of intravenous remifentanil PCA with epidural analgesia. Twenty parturients were randomised to receive intravenous patient-controlled analgesia with remifentanil or epidural analgesia. After one hour, pain scores had decreased significantly in both groups (remifentanil: -3.8 ± 2.6, $P<0.001$; epidural -6.7 ± 2.0, $P<0.01$). The decrease in pain scores was significantly greater in the epidural group at all interval times. In the remifentanil group, after an initial decrease, pain scores increased over time; within 2 hours, pain scores were no longer significantly different from baseline scores. By contrast, in the epidural group the decrease in pain scores was sustained. Mean maternal oxygen saturation was significantly lower in the remifentanil group after one hour of treatment compared to the epidural group (95.2 ± 2.4% vs. 99.0 ± 1.1%, $P<0.01$). In conclusion, in the 20 patients recruited to this study, pain relief in labour with epidural analgesia was more effective than with intravenous remifentanil patient-controlled analgesia.

One disadvantage of epidural analgesia is a possible increase in maternal temperature, which frequently results in the unnecessary administration of antibiotics during labour and the presumed diagnosis and treatment of neonatal sepsis. Adverse effects of remifentanil resemble those of other potent opioid analgesics and include respiratory depression with oxygen desaturation and sedation. In **chapter 4** we investigated side effects of epidural analgesia and remifentanil PCA. Parturients requesting analgesia were randomly assigned to receive remifentanil patient controlled or epidural analgesia. Control patients consisted of parturients not requesting pain medication. The primary objective was to compare incidence of maternal fever (temperature ≥38 °C); the secondary outcomes included incidence of low oxygen saturation, pain scores, nausea/vomiting, sedation scores, pruritus and neonatal outcome. Data from 140 parturients were analysed, 49 received remifentanil analgesia, 49 epidural analgesia and 42 no analgesia (controls). Fever (temperature ≥38 °C) developed in 10% of patients on remifentanil compared to 37% of patients on epidural analgesia and 7% of control patients ($p < 0.001$). One or more hypoxaemic events (oxygen saturation < 90% for at least 1 min) occurred in 48% of patients on remifentanil versus 15% of patients on epidural analgesia and 20% of control patients ($p = 0.003$). Although pain intensity scores differed significantly between remifentanil and epidural treatments in favour of the epidural, satisfaction was similar in both groups (remifentanil: 8.1 ± 1.2 versus epidural: 8.4 ± 1.2). Remifentanil analgesia was further associated with higher incidences of nausea and deeper levels of sedation. The differences in hemodynamic parameters between treatments were small and clinically irrelevant. To conclude, during treatment of labour pain, epidural analgesia is associated with a higher incidence of maternal fever, while remifentanil analgesia results in more frequent and deeper hypoxaemic events.

In order to better understand the effect of remifentanil PCA during labour on ventilation, rather than on surrogate markers of ventilation such as oxygen saturation, we performed a pharmacokinetic pharmacodynamic modelling and simulation study in **chapter 5**, using data from a previous study on the effect of iv remifentanil on ventilation in healthy volunteers. Simulations focused on the interaction between high-inspired oxygen (50%) and remifentanil, and the effect on ventilation. The results showed that high inspired oxygen affected the blood-effects-site equilibration half-life ($t_{1/2}ke0$) of remifentanil, increasing the speed of its onset/offset causing deeper nadirs in ventilation.
Additionally, a pain component was incorporated to take the hyperventilatory effect of pain into account. Pain seemed to cause an increase in baseline ventilation by about 50%.

In conclusion, high-inspired oxygen increases the speed of onset/offset of effect on ventilation of remifentanil, causing more pronounced reductions in ventilation.

In **chapter 6** we concentrated on safety of remifentanil PCA in a systematic review. Databases of Pubmed, EMBASE and Cochrane Library were searched for randomised controlled trials and observational trials that compared side effects of remifentanil to any other labour analgesic. The primary outcome was incidence of oxygen saturation (SpO2) less than 95% in parturients during treatment with remifentanil PCA. Secondary outcomes included other maternal side effects like nausea and sedation and effects on the neonate. Sixteen trials were identified for inclusion comparing either remifentanil to epidural analgesia (EA) or remifentanil to another opioid, either fentanyl or pethidine. Compared to EA remifentanil treatment was clearly associated with a higher risk for saturation levels below 95% (RR 3.12, 95% CI 2.37-4.11), while compared to fentanyl or pethidine the risk was similar to remifentanil (n = 162; RR 1.57, 95% CI 0.95-2.61). Of the secondary outcomes remifentanil caused more nausea and sedation than EA. Other outcomes did not differ between treatments. We concluded while remifentanil was comparable to other opioids with respect to maternal and neonatal outcomes, compared to epidural analgesia more toxicity was seen, in particular more oxygen desaturations and sedation. The results suggested that the safety of epidural analgesia is superior to that of remifentanil in labour analgesia.

FUTURE PERSPECTIVES

Epidural analgesia is considered 'gold standard' in obstetric analgesia, but there are situations in which epidural analgesia is contra-indicated, undesired or unavailable. An often used alternative is intramuscular pethidine, which is considered to have more sedative qualities then it has analgesic efficacy during labour. More alternatives for pain relief during labour are needed. Intravenous remifentanil seems interesting, given its unique pharmacokinetic profile with a short terminal half-life and rapid onset of action. Efficacy studies show better results for remifentanil compared to other opioids. Compared to epidural analgesia the analgesic quality is inferior. We confirmed this in chapter 2 and 3 showing better efficacy for remifentanil compared to pethidine and to fentanyl. However, the effect was time-limited. Approximately, within 3 hours after initiation pain scores returned to pre-treatment values. Epidural analgesia provided better analgesia and at a constant level, contrary to remifentanil. Against this background, there seems to be a place for remifentanil during labour, but it is

not comparable to neuraxial analgesia. Because of the time-limited effect, it is likely that multiparous women and women in the last phase of cervical dilation will benefit the most. More studies are needed to review the efficacy and satisfaction in these subgroups.

However, more important, is the safety of the analgesic. Remifentanil is a potent opioid, administered intravenously. Several adverse effects have been found; sedation, nausea, low respiratory rate and most importantly more oxygen desaturation (chapters 4, 5 and 6). Most concerning of all is the potential of a respiratory depression, which can have severe consequences for both mother and baby. In chapter 4 we established that hypoxaemic events (oxygen saturation < 90% for at least 1 min) occurred in almost half of the parturients on remifentanil. Several case reports described serious incidents during administration of remifentanil on the labour ward; in three cases a respiratory arrest occurred while in two cases a cardio-respiratory arrest was described.[1-5] No maternal or fetal death was reported.
Given these findings there only seems to be a place for remifentanil when safety is guaranteed. In 2014, the Dutch College of Obstetricians and Gynaecologists (NVOG) and the Dutch College of Anesthesiologists (NVA) have made a start by developing a Standard Operating Procedure for safe use of remifentanil during labour. This SOP focuses on the importance of maternal observations and responsibilities of the obstetric and anesthetic caregivers. The first aim is to evaluate the implementation of this SOP. After evaluation of this SOP it will be clear if the safety measurements are feasible in daily practice. Another important goal is the revision of the guideline of obstetric analgesia.
Ideally, there would be an anesthesiologist at the delivery rooms at all times in case of a severe adverse event. This is not accomplishable in current Dutch hospital practice. This means obstetricians, midwives and nurses should be well and frequently trained to act in case of a respiratory depression. Concerning monitoring, there should be one-to-one nursing to evaluate sedation levels, respiratory rates and oxygen saturation. It is questionable if pulse oximetry is sufficient to detect an apneic event. End-tidal carbon oxide concentration measurement may be beneficial. It is uncertain if this measurement is applicable for women in labour. More or other monitoring methods need to be employed in this group. This should be subject of future research.

In conclusion, remifentanil during labour is an option, but only if all monitoring conditions and safety requirements are met.

CONCLUSIONS

1. Remifentanil PCA provides superior analgesia compared to pethidine and fentanyl PCA, but the effect is time-limited.

2. Epidural analgesia is superior to remifentanil in analgesic efficacy and provides a constant level of pain relief. During administration of remifentanil pain scores increase over time.

3. Remifentanil PCA is associated with more hypoxaemic events, sedation and nausea compared to epidural analgesia.

4. High-inspired oxygen increases the speed of onset and offset of the effect of remifentanil on respiration, consequently causing more pronounced reductions in ventilation.

5. Remifentanil is comparable to pethidine and fentanyl with respect to maternal and neonatal outcomes.

6. Because of safety concerns with respect to respiratory depression careful continuous monitoring of maternal saturation, respiratory rates and sedation levels are required.

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Chapter 8

Samenvatting, toekomst-perspectieven en conclusies

SAMENVATTING, TOEKOMSTPERSPECTIEVEN EN CONCLUSIES

Het doel van deze thesis was evaluatie van het pijnbestrijdend effect en veiligheid van remifentanil tijdens de bevalling.

In **hoofdstuk 2** wordt de werkzaamheid van remifentanil vergeleken met pethidine en fentanyl gedurende de bevalling. Honderd negenenvijftig parturiënten werden gerandomiseerd tussen remifentanil, pethidine of fentanyl. De opiaten werden intraveneus toegediend via een "Patient Controlled Analgesia" methode (PCA). De resultaten toonden een klein tot matig effect op de pijnstilling aan bij gebruik van remifentanil (gemiddelde pijnscores bleven boven 4,5 in alle groepen). Pijnscores in de remifentanil groep waren gemiddeld lager in vergelijking tot pethidine en fentanyl, maar alleen gedurende het eerste uur van de behandeling. In alle groepen keerden pijnscores binnen drie uur na het begin van de behandeling terug naar het niveau van voor de toediening. Het effect lijkt derhalve gelimiteerd qua tijd. Remifentanil was geassocieerd met significant meer episodes van maternale zuurstofsaturatie < 95%, meer sedatie en meer jeuk. Er werden geen verschillen gevonden in neonatale uitkomst. Concluderend, de werkzaamheid van pethidine, fentanyl en remifentanil PCA tijdens de bevalling varieerde qua grootte van een klein tot een matig effect. Het pijnstillend effect van remifentanil PCA was beter dan dat van pethidine en fentanyl PCA, maar alleen gedurende het eerste uur van de behandeling. In alle groepen keerden pijnscores binnen drie uur na begin van de behandeling terug naar uitgangswaardes.

Epidurale analgesie wordt beschouwd als de 'gouden standaard' op het gebied van de obstetrische analgesie. In **hoofdstuk 3** vergelijken we de effectiviteit van intraveneuze remifentanil PCA met epidurale analgesie. Twintig parturiënten werden gerandomiseerd tussen remifentanil PCA en epidurale analgesie. Een uur na start van de pijnmedicatie werd een significante daling van pijnscores gezien in beide groepen (remifentanil: -3,8 ± 2,6, $p < 0,001$; epidurale analgesie -6,7 ± 2,0, $p < 0,01$). De daling van de pijnscores was significant groter in de epiduraal groep op alle gemeten tijdstippen. In de remifentanil groep namen pijnscores na verloop van tijd weer toe. Binnen 2 uur waren pijnscores niet langer significant verschillend ten opzichte van de uitgangswaardes. Daarentegen bleven pijnscores in de epiduraal groep continu laag. Een uur na start van de pijnmedicatie was de gemiddelde maternale zuurstofsaturatie in de remifentanil groep significant lager dan in de epidurale groep (95,2 ± 2,4% versus 99,0 ± 1,1%, $p < 0,01$). Concluderend, in deze studie was de pijnstilling tijdens de

bevalling via epidurale analgesie effectiever dan remifentanil (PCA).

Een nadeel van epidurale analgesie is een mogelijke stijging van de maternale temperatuur; dit resulteert regelmatig in onnodige toediening van antibiotica tijdens de bevalling en een verdenking op en behandeling van neonatale sepsis. Nadelige effecten van remifentanil zijn vergelijkbaar met die van andere potente opiaten, waaronder maternale zuurstofdesaturatie, respiratoire depressie en sedatie. In **hoofdstuk 4** onderzoeken we de bijwerkingen van epidurale analgesie en van remifentanil PCA.
Parturiënten met een pijnstillingsverzoek werden gerandomiseerd tussen remifentanil PCA en epidurale analgesie. De controle groep (niet gerandomiseerd) bestond uit parturiënten die niet om pijnstilling vroegen. De primaire uitkomst was het vergelijken van de incidentie van maternale koorts (temperatuur ≥38 °C); secundaire uitkomsten waren incidentie van lage maternale zuurstofsaturatie, pijnscores, misselijkheid en/of braken, sedatiescores, jeuk en de neonatale uitkomst. Gegevens van 140 parturiënten werden geanalyseerd; 49 ontvingen remifentanil PCA, 49 ontvingen epidurale analgesie en 42 parturiënten ontvingen geen pijnstilling (controlegroep). Tien procent van de patiënten in de remifentanil groep ontwikkelde koorts vergeleken met 37% van de parturiënten in de epiduraal groep. Zeven procent van de controlepatiënten ($p < 0,001$) ontwikkelde koorts. Bij 48% van de parturiënten in de remifentanil groep traden een of meer episodes van hypoxie (zuurstofsaturatie < 90% gedurende ten minste 1 min) op *versus* 15% in de epidurale analgesie groep *versus* 20% in de controlegroep ($p = 0,003$). Hoewel er een aanzienlijk verschil was tussen pijnscores in de remifentanil- en de epiduraalgroep in het voordeel van de epiduraalgroep, was de tevredenheid vergelijkbaar tussen beide groepen (remifentanil: 8,1 ± 1,2 versus epiduraal: 8,4 ± 1,2). Tijdens toediening van remifentanil PCA werd meer misselijkheid en meer sedatie gezien. De verschillen in hemodynamische parameters waren klein en klinisch niet relevant. Concluderend, epidurale analgesie is geassocieerd met het vaker optreden van maternale koorts, terwijl remifentanil resulteert in frequentere en diepere episodes van hypoxie.

Om het effect van remifentanil PCA op de ventilatie in vrouwen *durante partu* beter te begrijpen, hebben we een farmacokinetische-farmacodynamische analyse en simulatiestudie uitgevoerd, welke is beschreven in **hoofdstuk 5**. Hiervoor werden gegevens gebruikt uit een eerdere studie naar het effect van intraveneuze remifentanil op ventilatie in gezonde vrijwilligers. De simulaties richtten zich op de interactie tussen hoge inspiratoire zuurstofconcentraties (50%) en remifentanil uitgedrukt in het

effect op ventilatie. De resultaten lieten zien dat door gebruik van 50% zuurstof de halfwaardetijd ($t_{1/2}ke0$) van het blood-effect-site equilibrium van remifentanil beïnvloed werd, waardoor de onset en offset van remifentanil versneld werden en de nadir in ventilatie verlaagd werd.
Er werd tevens een pijncomponent geïncorporeerd om rekening te houden met het hyperventilatoire effect van pijn. Pijn leidde tot een verhoging van de uitgangsventilatie met 50%.
Concluderend, een hoge inspiratoire zuurstofconcentratie versnelt de onset en offset van het effect op ventilatie door remifentanil, wat leidt tot een sterkere afname van ventilatie.

In **hoofdstuk 6** wordt verder ingegaan op de veiligheid van remifentanil PCA in een systematische review. We hebben in de databases van Pubmed, EMBASE en de Cochrane Library gezocht naar gerandomiseerde en observationele studies waarin bijwerkingen van remifentanil vergeleken werden met die van andere pijnmedicatie durante partu. De primaire uitkomst was de incidentie van zuurstofsaturatie (SpO_2) onder 95% in parturiënten tijdens behandeling met remifentanil. Secundaire uitkomsten waren maternale bijwerkingen zoals misselijkheid, sedatie en effecten op de neonaat. Zestien studies kwamen in aanmerking voor inclusie; in deze studies werd remifentanil vergeleken met epidurale analgesie of met een ander intraveneus of intramusculair opiaat; fentanyl of pethidine. Vergeleken met epidurale analgesie werd in de remifentanil groep meer zuurstofsaturatie onder 95% (RR 3,12, 95% CI 2,37-4,11) gezien, terwijl vergeleken met fentanyl en pethidine het risico op desaturatie vergelijkbaar was (n = 162, RR 1,57, 95% CI 0,95-2,61). Behandeling met remifentanil leidde tot meer misselijkheid en sedatie dan behandeling met epidurale analgesie. Andere secundaire uitkomsten lieten geen verschil zien tussen de behandelingen. Op het gebied van maternale en neonatale uitkomsten was remifentanil derhalve vergelijkbaar met andere opiaten. In vergelijking tot epidurale analgesie werden meer bijwerkingen gezien, met name meer en diepere zuurstofdesaturaties en meer sedatie. Deze resultaten laten zien dat de veiligheid van epidurale analgesie superieur is aan die van remifentanil tijdens de bevalling.

TOEKOMSTPERSPECTIEVEN

Epidurale analgesie wordt beschouwd als de 'gouden standaard' in de obstetrische analgesie, maar er zijn situaties waarin epidurale analgesie gecontraïndiceerd,

ongewenst of niet beschikbaar is. Een veelgebruikte alternatief is pethidine intramusculair, echter pethidine lijkt meer sedatie te geven dan dat het effectieve pijnbestrijding levert tijdens de bevalling. Er zijn derhalve meer alternatieven nodig. Intraveneuze remifentanil lijkt interessant, gezien het unieke farmacokinetische profiel met een snelle werking en een korte halfwaardetijd. Studies naar werkzaamheid tonen betere resultaten van remifentanil in vergelijking met andere opiaten. Vergeleken met epidurale analgesie is het pijnstillend effect minder. Dit wordt aangetoond in hoofdstuk 2 en 3 waarin de mate van pijnstilling van remifentanil beter is dan dat van pethidine en fentanyl. Het effect is echter kortdurend. Binnen 3 uur na de start van de pijnstilling zijn pijnscores terug op het niveau van voor de start. Epidurale analgesie geeft betere en meer constante pijnstilling, in tegenstelling tot remifentanil.
In dit licht lijkt er een plaats te zijn voor het gebruik van remifentanil tijdens de bevalling, maar het opiaat is niet vergelijkbaar met epidurale analgesie. Vanwege het kortdurende effect van remifentanil, is het waarschijnlijk dat multipara en vrouwen in de laatste fase van de ontsluiting het meest baat hebben bij het middel. Meer studies zijn nodig om de effectiviteit en de tevredenheid in deze subgroepen te bekijken.

Belangrijker is echter de veiligheid van het analgeticum. Remifentanil is een potent opiaat en wordt intraveneus toegediend. Er zijn meerdere bijwerkingen geobserveerd; sedatie, misselijkheid, een lage ademfrequentie en zuurstof desaturatie (hoofdstuk 4, 5 en 6). De meest zorgwekkende potentiële complicatie is een respiratoire depressie, welke ernstige gevolgen kan hebben voor zowel de moeder als de baby. In hoofdstuk 4 hebben we vastgesteld dat in bijna de helft van de parturiënten met remifentanil hypoxie (zuurstofsaturatie <90% gedurende ten minste 1 min) optreedt. Er zijn verschillende "case reports" verschenen waarin ernstige incidenten tijdens de toediening van remifentanil zijn beschreven; in drie gevallen trad een ademhalingsstilstand op en in twee gevallen was er sprake van een cardiorespiratoir arrest.[1-5] Er zijn geen gevallen van maternale of foetale sterfte bekend.
Gezien deze bevindingen lijkt er alleen plaats voor remifentanil te zijn wanneer de veiligheid gegarandeerd kan worden. In 2014 hebben de Nederlandse Vereniging van Obstetrie en Gynaecologie (NVOG) en de Nederlandse Vereniging van Anesthesiologie (NVA) een begin gemaakt met het ontwikkelen van een Standard Operating Procedure voor het veilig gebruik van remifentanil tijdens de bevalling. Deze SOP richt zich op het belang van het observeren van de aanstaande moeder en op de verantwoordelijkheden van obstetrische en anesthesiologische zorgverleners. De implementatie van de SOP dient nu eerst geëvalueerd te worden. Na deze evaluatie zal duidelijk worden of de veiligheidsmaatregelen haalbaar zijn in de dagelijkse praktijk. Een ander belangrijk

doel is herziening van de richtlijn medicamenteuze pijnbestrijding tijdens de bevalling. Idealiter zou er te allen tijde een anesthesioloog op de verlosafdeling aanwezig moeten zijn om in te grijpen in geval van een ernstige complicatie. Dit is echter niet haalbaar in de huidige Nederlandse setting. Dit betekent dat obstetrici, verloskundigen en verpleegkundigen regelmatig en goed moeten worden getraind om te kunnen handelen in geval van een ernstige ademdepressie en een (cardio)respiratoir arrest. Wat betreft de monitoring, is het noodzakelijk om één-op-één verpleegkundige zorg te bieden zodat continu sedatie niveau, ademfrequentie en zuurstofsaturatie betrouwbaar geëvalueerd kan worden. Het is de vraag of vingerpulsoximetrie alleen voldoende is om een apneu te detecteren. Capnografie zou mogelijk een goede aanvulling kunnen zijn. Het is echter onzeker of deze meting toepasbaar is tijdens de bevalling. Andere opties voor bewaking van deze groep zouden onderwerp moeten zijn van toekomstig onderzoek.

Concluderend, het gebruik van remifentanil tijdens de bevalling is een optie, maar alleen als aan alle bewakingsvoorwaarden en veiligheidseisen kan worden voldaan.

CONCLUSIES

1. Remifentanil PCA geeft betere pijnbestrijding dan pethidine en fentanyl PCA, maar het effect is kortdurend.

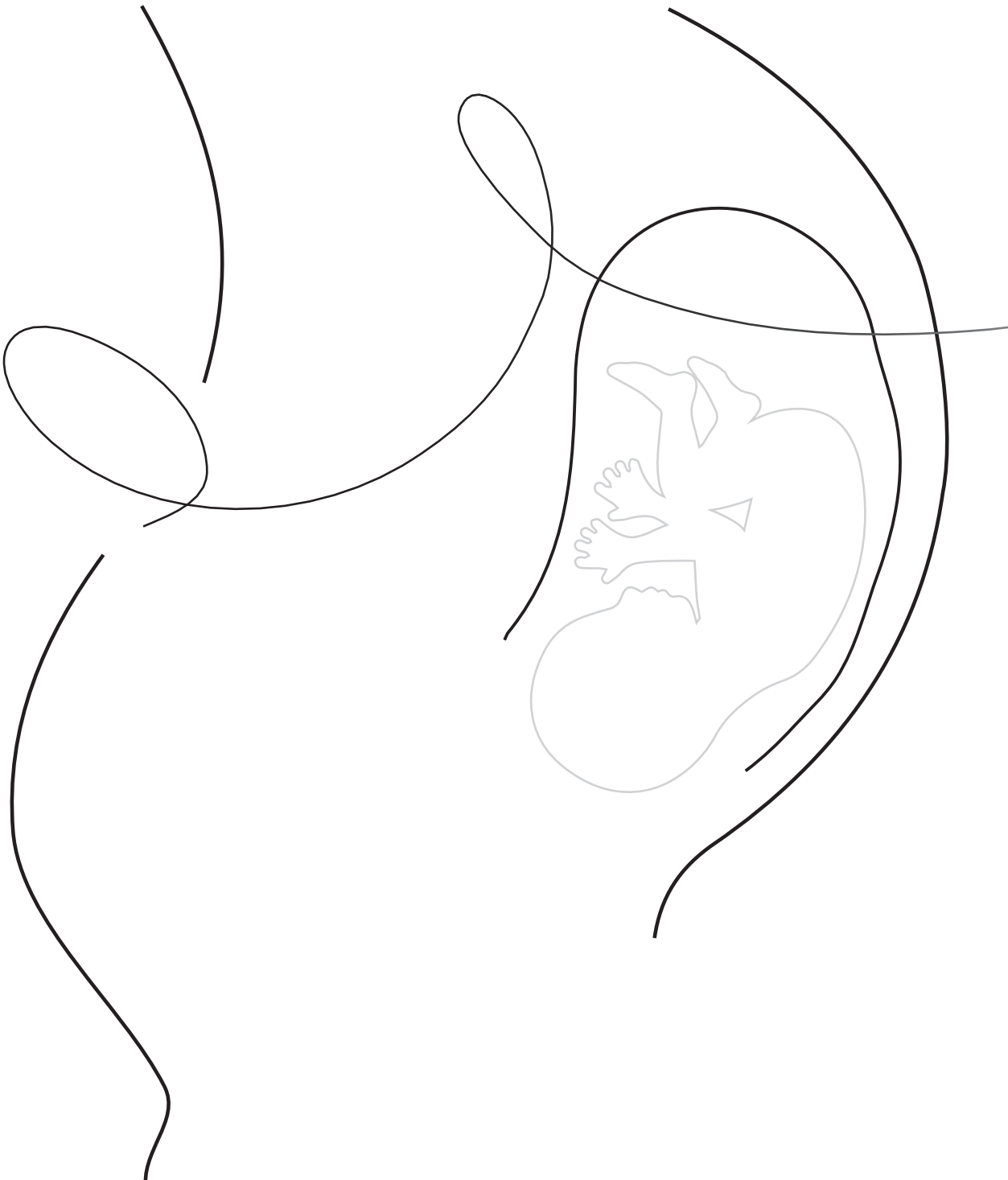
2. Epidurale analgesie geeft betere pijnbestrijding dan remifentanil en zorgt voor een constant niveau van pijnbestrijding in tegenstelling tot remifentanil, waarbij pijnscores toenemen na verloop van tijd.

3. Remifentanil PCA is geassocieerd met meer episodes van hypoxie, sedatie en misselijkheid in vergelijking tot epidurale analgesie.

4. Een hoge inspiratoire zuurstofconcentratie versnelt de onset en offset van het effect op ventilatie door remifentanil; dit leidt tot een sterkere afname van ventilatie.

5. Remifentanil is vergelijkbaar met pethidine en fentanyl met betrekking tot maternale en neonatale uitkomsten.

6. In verband met het risico op een ademhalingsdepressie is een strikte en continue bewaking van de maternale saturatie, ademhaling en sedatie vereist.



Chapter 9

Curriculum Vitae
Publications
Acknowledgments/Dankwoord

Curriculum Vitae

Marit Douma, born July 21st 1980 in Leeuwarden, earned her VWO degree at the Nieuwediep in Den Helder. She was awarded her masters degree in Medicine from the University of Leiden in 2005.

She then worked as a physician at the department of Obstetrics and Gynaecology at the Kennemer Gasthuis in Haarlem, followed by a position at the Bronovo hospital in The Hague.
In 2008 she started her residency in Obstetrics and Gynaecology at the Leiden University Medical Center (LUMC), Leiden and Haga hospital, The Hague (2008 – 2014) (prof. dr. J.M.M van Lith, dr. E.J. van Rijssel, dr. B.W.J. Hellebrekers). The research described in this thesis (prof. dr. A. Dahan, prof. dr. J.M.M van Lith) was combined with her residency.
In 2015 she joined the Department of Obstetrics and Gynaecology at the Ikazia hospital in Rotterdam as a staff member where she completed her thesis.
From January 2017 she will be a staff member at the Haga hospital in The Hague.

She currently lives in The Hague with Casper van Pijpen, and their three daughters Flore (2011), Annemijn (2013) and Philine (2016).

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