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Petri Volmanen

INTRAVENOUS PATIENT CONTROLLED ANALGESIA WITH REMIFENTANIL IN EARLY LABOUR

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Abstract

In four prospective clinical trials, 114 parturients used intravenous patient-controlled remifentanil analgesia during the 1st stage of labour. The median effective dose per bolus was ascertained to be 0.4 µg/kg and the pain scores were reduced with this by a median of 2 on a numerical scale (0–10). Compared with nitrous oxide, 15 parturients included in a cross-over study reported a larger reduction in pain scores during remifentanil analgesia (1.5 vs. 0.5, $p = 0.001$) and better pain relief scores (2.5 vs. 0.5 on a ranked five point scale 0–4, $p < 0.001$). In a parallel study including 45 parturients, epidural analgesia (EDA, 20 ml bupivacaine 0.625 mg/ml and fentanyl 2 µg/ml) was associated with lower pain scores (5.2 vs. 7.3 with remifentanil, $p = 0.004$) but variables related to satisfaction with analgesia (pain relief score, proportion of mothers with desire to continue with the given medication and termination of the study due to inadequate pain relief) were similar. A comparison of two methods for timing the remifentanil bolus during the uterine contraction cycle suggested that delaying the bolus does not improve analgesia. A period effect was noted in the cross-over trial with higher pain scores and increased drug consumption during the second study period suggesting acute hyperalgesia.

Side effects of remifentanil analgesia included respiratory depression warranting oxygen supplementation in 33% of parturients. Sedation was experienced by the parturients using remifentanil and this was scored as stronger than sedation during nitrous oxide and EDA. The number of parturients with nausea did not increase during remifentanil analgesia. Other maternal side effects included dizziness, a difficulty in visual focusing and itching. Foetal heart rate tracing abnormalities were noted. The incidence of abnormal tracings and decreased UapH were not different, however, from that observed during nitrous oxide or EDA. Apgar scores at 1 and 5 minute indicated no neonatal depression.

Keywords: first stage labour, labour pain, obstetric analgesia, opioid analgesics, pain measurement, patient-controlled analgesia, piperidines

To Pia,

Johannes, Johanna, Sonja, Joni, Daniel ja Nea

Syntymä on kova juttu, tulla läpi luisen
tiuhan veräjän veripahka päässä, nivel sijoiltaan,
suu, silmät täynnä verta, limaa, virtsaa, tukehtua,
tekohengitystä, riippua pää alaspäin, lyöntejä,
tyhjä ontto ilma ympärillä, melu, haju,
hehkulamppu, laapista silmään, rääkätty
tajuton nainen, kirkas veitsi kuin hitsausliekki,
lääkärin ja hoitajattarien Ku Klux Klan.

Veijo Meri

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Abbreviations

BE	Base excess
bpm	Beats per minute
CS	Caesarean section
CSE	Combined spinal epidural
CTG	Cardiotocogram
Cx	Uterine cervical dilation
ED_{95}	Effective dose for the 95th percentile
$ETCO_2$	End tidal carbon dioxide
ETN_2O	End tidal nitrous oxide
EDA	Epidural analgesia
FHR	Foetal heart rate
fMRI	Functional magnetic resonance imaging
HR	Heart rate
IM	Intramuscular
IT	Intrathecal
IV	Intravenous
IVPCA	Intravenous patient controlled analgesia
LOR	Loss of resistance
MA	Maternal artery
MAP	Mean arterial pressure
MLAC	Minimum local analgesic concentrations
MOAA	Modified Observer's Assessment of Alertness
MPQ	McGill Pain Questionnaire
N_2O	Nitrous oxide
NIBP	Non-invasive blood pressure
NMDA	N-methyl-D-aspartic acid
NRS	Numerical rating scale
NS	Not statistically significant
PCA	Patient controlled analgesia
PID	Pain intensity difference
PONV	Postoperative nausea and vomiting
RCT	Randomised controlled trial
RR	Relative risk
SaO_2	Haemoglobin oxygen saturation
SAP	Systolic arterial pressure

TCI	Target controlled infusion
UA	Umbilical artery
UAPh	Umbilical artery Ph
UpH	Umbilical cord pH
UV	Umbilical vein
VAS	Visual analogue scale
VRS	Verbal rating scale

List of original publications

I Volmanen P, Akural EI, Raudaskoski T & Alahuhta S (2002) Remifentanil in obstetric analgesia: a dose-finding study. Anesth Analg 94: 913–917.

II Volmanen P, Akural EI, Raudaskoski T, Ohtonen P & Alahuhta S (2005) Comparison of remifentanil and nitrous oxide in labour analgesia. Acta Anaesthesiol Scand 49: 453–458.

III Volmanen P, Sarvela J, Akural EI, Raudaskoski T, Korttila K & Alahuhta S (2008) Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study. Acta Anaesthesiol Scand 52: 249–255.

IV Volmanen P, Akural E, Raudaskoski T, Ranta P, Tekay A, Ohtonen P & Alahuhta S (2010) IVPCA with remifentanil bolus during the contraction pause does not improve the analgesic effect, during early labour. Manuscript

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1 Introduction

Epidural analgesia (EDA) and combined spinal-epidural (CSE) analgesia are well established in developed countries and provide high-quality pain relief for millions of parturients every year. Nevertheless there are many women who do not have this choice for one reason or another. In the world at large, the major drawback of regional techniques is that they are expensive and their safe use requires an anaesthetist and a developed hospital. Variation in the use of epidural analgesia in Finland also suggests that this method is not equally available to all parturients. Even in those centres where neuraxial analgesia is used, there is not yet an effective and safe alternative for parturients with contraindications to regional analgesia. An alternative method for relieving labour pain might also be useful in those cases which refuse to use neuraxial analgesia, in rapidly progressing labour when other effective methods are not readily available, and for parturients who request pain relief during the early stage of labour when more invasive forms of analgesia may not be justified.

Remifentanil is an agonist of the μ-receptor which has been routinely used in surgical anaesthesia and postoperative analgesia for more than a decade. Its unique features, fast onset of effect and short elimination by tissue esterases with no accumulation after even long infusions or repeated boluses, have made it popular in long procedures when fast recovery is the goal. It is also an integral part of the medication used for total intravenous anaesthesia. Remifentanil has not been licensed, however, for use in obstetric analgesia. To the best of this author's knowledge, the manufacturers of remifentanil have no plans at present to apply for a licence for its use in obstetric anaesthesia. Failure to apply for a licence to use a drug in pregnancy is not unusual due to the high cost involved, as well as the limited economic return and potential risks in this area of medicine (Eisenach 1999).

This academic dissertation attains to fulfil its part in the scientific community by examining the basic pharmacology of remifentanil in obstetrics, determining the appropriate sub-group of parturients who will most benefit from the drug, and by ensuring that all necessary precautions are established. It is hoped that the information obtained on the use of remifentanil in obstetric analgesia in the four original studies of this investigation will contribute to the shift necessary in the global perception of this drug to metamorphise remifentanil labour analgesia from an experimental adventure to a method used in routine practice. Once all the

prerequisite information and experience has been gathered, the use of remifentanil in labour rooms may well prove beneficial to many patients.

2 Review of literature

2.1 Remifentanil

Remifentanil is a μ-receptor agonist, which has been used routinely in surgical anaesthesia and postoperative analgesia since 1996. Kan *et al.* (1998) studied the basic pharmacokinetics of remifentanil given as an adjunct to epidural anaesthesia for caesarean section. Remifentanil was introduced into obstetric analgesia shortly after this, which was reflected in the publication of the first case reports of effective IV remifentanil analgesia during labour (Brada *et al.* 1998, Jones *et al.* 1999, Thurlow & Waterhouse 2000, Roelants *et al.* 2001).

A rapid manual bolus of ≤ 0.5 μg / kg at the onset of every uterine contraction was employed in a preliminary study, which attempted to determine a suitable dosage regimen for remifentanil in labour pain. The study was terminated early because of significant maternal side effects in the absence of effective pain control (Olufolabi *et al.* 2000). In contrast with this, another study showed better results. Thirteen of 21 (62%) women chose to continue using remifentanil intravenous patient controlled analgesia (IVPCA) up to and during delivery. Nineteen out of 21 (90%) achieved a reduction in pain scores from baseline (Blair *et al.* 2001). A study employing an intravenous target-controlled infusion (TCI) also suggested that remifentanil provides considerable pain relief in labour (Viviand *et al.* 2003).

The advantages of remifentanil include ultra-short elimination and titratability to individual needs. In the general population, the context-sensitive half-time - i.e. the time needed for a 50% reduction of the concentration in blood after the cessation of infusion that maintains a steady state – is 3 minutes (Kapila *et al.* 1995). The pharmacokinetic study made during anaesthesia for caesarean section showed greater clearance of remifentanil in parturients compared with healthy non-pregnant volunteers (Kan *et al.* 1998). Remifentanil readily crosses the placenta with an umbilical vein (UV) to maternal artery (MA) concentration ratio of 0.73–0.88. There is either rapid metabolism of the drug in the foetus or a large volume of distribution as the umbilical artery (UA): UV is 0.29–0.6, both of these mechanisms being consistent with the pharmacokinetics of remifentanil in neonates (Kan *et al.* 1998, Ngan Kee *et al.* 2006, Ross *et al.* 2001).

The short elimination time provides substantial advantages in terms of obstetric use. The time from dose to delivery is difficult to predict, and the usual

profile of pain during labour and delivery is associated with an increased requirement for analgesic efficacy as labour progresses (Capogna *et al.* 1998). Only analgesics with a profile of innocent side effects - such as properly administered modern local anaesthetics - or a very short elimination can be used effectively and safely in case of sudden delivery (Lyons and Reynolds 2001). Remifentanil appears to fall into the latter category. In contrast with other opioids, the rapid elimination of remifentanil also makes it possible to down-titrate the dose in a short time. In one case, an initial PCA bolus of 75 μg (approximately 1.0 μg/kg) was found to cause excessive maternal sedation and early decelerations in the foetal heart rate (FHR) tracing. These side effects subsided when the PCA bolus was reduced to 0.5 μg/kg (Brada *et al.* 1998).

It is generally observed that the dose of systemic opioids needed for postoperative analgesia shows large inter-individual variability. For example, the lowest blood concentration of sufentanil after comparable gynaecological procedures has been shown to be 50 times less than the maximum during effective PCA analgesia (Lehman *et al.* 1991). Many factors are probably associated with this variation, one of them being genetic variation in the structure of the opioid receptors (Landau *et al.* 2008). The range of opioid concentrations resulting in effective analgesia in labour pain may be even wider, as the individual perception of ideal labour pain may vary considerably from one parturient to another.

A variety of methods has been used for administering IV remifentanil to the parturient. To date, no comparisons have been made to show that any of the methods used in the published reports – PCA boluses, baseline infusion combined with PCA boluses, or TCI – is superior to any of the others. It appears, however, that very fast manual boluses given at the beginning of each contraction failed to produce adequate pain relief, while simultaneously producing an excess of side effects (Olufolabi *et al.* 2000). The reason for this could be that the peak at the effect-site coincided with the pause between contractions.

In computerised simulations of effect-site concentrations, the half-time required for blood effect-site equilibration was found to be as long as 1.3–1.6 minutes for remifentanil (Egan *et al.* 1996). In accordance with this, Leppä *et al.* (2006) observed an onset of functional magnetic resonance imaging (fMRI) signal at 20–30 s with a maximum between 80 and 90 s in the fastest loci in the brain after remifentanil administration. The time to maximum ventilatory depression appeared to be 2.5 minute in a study by Babenco *et al.* (2000).

While the concentration or remifentanil in the blood appears to decrease very rapidly regardless of the duration of the preceding infusion, the time required for equilibration between the blood and the effect-site results in a somewhat slower disappearance of the pharmacologic effects. In healthy volunteers, the analgesic effect appeared to be reduced to a half in 6 minutes (Glass *et al.* 1993). In a fMRI study, Wise *et al.* (2004) noted a somewhat shorter half time for the offset of the action (3.07 minutes). After termination of the drug infusion, a 50% recovery in minute ventilation was observed in 5.4 minutes (Kapila *et al.* 1995).

When the difficulty in anticipating uterine contractions and the 70-second perceivable duration of a single uterine contraction (Brasted & Callahan 1984, Caldeyro-Barcia & Poseiro 1960) is taken into account, one could suggest that the lag between the peak concentration in the blood and the peak concentration at the effect-site would make it impossible to provide analgesia with a single PCA bolus during the peak of the pain of the contraction for which the PCA signal is given. The delay in the disappearance of the effect makes it possible to relieve the pain of the second contraction and possibly even the third contraction by a single bolus of remifentanil given at the beginning of the first contraction in a series of contractions. Recently, some evidence has been published supporting the idea of trying to optimise drug delivery. Balcioglu *et al.* (2007) noted a better analgesia with IVPCA utilising a background infusion of 0.15 μg/kg/min compared with 0.1 μg/kg/min, although there was no difference in the consumption of remifentanil between the two dosing regimens. Balki *et al.* (2007) noted fewer side effects when background infusion was titrated according to the need instead of changes being made in the PCA dose.

The clinical studies concerning remifentanil in obstetric analgesia – excluding the original studies included in the present investigation – are summarised in table 1. Data concerning the consumption of remifentanil has been reported in 4 papers: Volikas et al. (2005) and Evron et al. (2008) reported a mean consumption of 0.12–0.14 μg/kg/min with IVPCA. Balcioglu *et al.* (2005) reported a mean consumption of 0.25–0.27 μg/kg/min, while D'Onofrio *et al.* (2009) noted the largest infusion rate used by parturients with a continuous median infusion of 0.075 μg/kg/min. Two papers give the median total dose/h and the mean weight of the parturients (Evron *et al.* 2005, Balki *et al.* 2007). Supposing that the median is not too far different from the mean, one could make an estimate that the average consumption was approximately 0.06–0.09 μg/kg/min in these studies.

Safety is the major issue in the adoption of remifentanil for clinical use in delivery rooms. During the clinical studies required for the initial registration of

remifentanil, several cases of respiratory depression and apnoea occurred when remifentanil was inadvertently infused, e.g. by flushing the intravenous line during administration of another drug or from residual remifentanil left in the tubing after discontinuation. For these reasons *inter alia*, the Food and Drug Administration approval in the United States was granted on condition that the label indicate that remifentanil can be used only in highly monitored settings (operating room or postoperative recovery room) under the supervision of an anaesthesia practitioner (Landow 1999).

Studies concerning remifentanil in obstetric analgesia have been reviewed in a pro and con discussion by Hill (2008a) and Van de Velde (2008) and at least five review articles concerning remifentanil in labour analgesia (Van de Velde 2005a, Evron & Ezri 2007, Hill 2008bc, Frambach *et al.* 2009, Hinova & Fernando 2009). The writers of a systematic review collected all published case reports and studies comprising 32 references relating the experiences of remifentanil use in 281 women in labour including three of the original articles in this dissertation with 56 cases of remifentanil analgesia included in the analyses of these three studies (Arnal *et al.* 2009). In addition to the papers included in the systematic review, four abstracts and two journal articles have been published concerning the use of remifentanil in labour analgesia including 93 parturients using IVPCA remifentanil with and without EDA and 205 parturients using continuous infusion (Evron *et al.* 2008, D'Onofrio *et al.* 2009). The abstracts include one small study concerning IVPCA and three large audits of the clinical use of remifentanil labour analgesia including 2332 deliveries (Hodginson & Hughes 2008 [n = 612], Harbers *et al.* 2008 [n = 305], Foley & Hill 2009 [n = 1374], Tveit & Rosland 2009 [n = 41]). In total – apart from the original studies of this dissertation – the papers and abstracts published to date include 2855 parturients receiving remifentanil during labour. It is a possibility that some parturients have been reported several times over due either to inclusion of the same material in several papers or to the parturients' readmission for separate pregnancies. Thus far, no case of maternal mortality or permanent disability has been reported.

To date, while there appears to have been a decline in the use of parenteral analgesia in developed countries (from 37–53% to 37–42% over 20 years in USA), an increase in the use of remifentanil IVPCA has been observed in Northern Ireland with a concomitant decline in the use of neuraxial methods (Bucklin *et al.* 2005, Foley & Hill 2009).

2.2 Epidural analgesia

After the lumbar epidural block using the loss-of-resistance (LOR) technique had been popularised by Dogliotti, its use was adapted in obstetric analgesia. Epidural blocks were also performed with the Gutierrez technique, which was based on the negative pressure in the epidural space with fluid moving inwards in an indicator attached to the needle once the ligamentum flavum was pierced. Graffagnino & Seyler (1938) described epidural analgesia aimed at analgesia during the 2nd stage of labour in 56 cases of vaginal delivery and in 10 cases of caesarean sections. The writers described two life threatening situations, one of which included the clinical death of the mother followed by a successful resuscitation with immediate caesarean section, artificial respiration, epinephrine and caffeine. It is interesting to note that in the beginning of the development of EDA, this method was used primarily to relieve pain during the 2nd stage of labour.

Flowers *et al.* (1949) reported the first continuous epidural block for obstetrics using a plastic tube inserted into the epidural space. Intrathecal and caudal blocks were only superseded by EDA in the clinical practice, however, after commercial epidural catheters came into widespread use in the 1970s (Chadwick 2005).

The use of EDA was also sparse in Finland until the 1970s when selective lumbar epidural blocks were provided in Oulu as a daytime service. In this method, an epidural catheter was inserted at the L1-L2 interspace and small boluses (average 4.6 ml) of 0.5% bupivacaine were given to block the nerve roots concerned in conveying pain impulses from the uterine cervix, to relieve pain during the 1st stage of labour only (Hollmén *et al.* 1977).

Since the discovery of spinal opioid receptors in the late 1970s, a combination of opioids and dilute local anaesthetics has become popular. The advantages of spinal opioids in EDA and CSE include a lesser degree of motor block due less local anaesthetic required and the benefits this has on the delivery outcome, i.e. a lower probability for instrumental delivery (Comparative Obstetric Mobile Epidural Trial Study group UK 2001, Robinson *et al.* 2001). A controversy has existed, however, as to whether the opioids administered into the epidural space actually work spinally or supraspinally through systemic absorption. Using a minimum local analgesic concentration (MLAC) -method, Polley *et al.* (2000) were able to show that there seems to be an advantage to the epidural administration compared with systemic administration - at least with fentanyl. An increased effect is noted with an increased volume in the epidural

bolus resulting in the ability to use ultradilute local anaesthetics (Robinson *et al.* 2001).

Neuraxial labour analgesia is widely available in developed countries with an increase of use reaching 57–77% of deliveries by 2001 in the USA (Bucklin *et al.* 2005). In Finland, the use of neuraxial labour analgesia increased from 8.2% in 1987 to 60.1% in 2008 (National Institute for Health and Welfare 2008).

2.3 Nitrous oxide

Originally introduced to medicine by Horace Wells, nitrous oxide was first reported in obstetric analgesia by Stanislav Klikowitsch as a mixture with oxygen (Klikowitsch 1881). This combination was rediscovered in the 1960's as the commercial product Entonox® which contains oxygen and nitrous oxide in equal proportions. The question of whether nitrous oxide could be used without supervision was raised in Britain at that time. A specific committee organised a multicenter study including 788 parturients which confirmed the safety of nitrous oxide outside the direct supervision by anaesthesia personnel (Committee on Nitrous Oxide and Oxygen Analgesia in Midwifery 1970).

In Nordic countries, nitrous oxide is mixed with oxygen in the labour room and administered using a PCA method. The parturient is advised to breath through a tight-fitting mask connected to a demand valve and continue breathing up to the point when the contraction pain begins to diminish. Rosen (2002) suggested a time lag of 50 seconds between the onset of breathing 50% nitrous oxide to its peak effect. Unfortunately, no details on pharmacodynamics were given. Einarsson *et al.* (1996) measured gas kinetics during the intermittent inhalation of 50% and 70% nitrous oxide, noting that at the end of an inhalation of 58 seconds, the end tidal nitrous oxide (ETN_2O) reached 36.3% and 54.5%, respectively. The concentration of nitrous oxide in exhaled gas diminished within 30 seconds after the intake was discontinued. In practice, it is difficult to obtain the peak effect with 50% nitrous oxide in oxygen during a single uterine contraction. It is possible that nitrous oxide is also eliminated quickly enough to not accumulate an analgesic effect over consecutive uterine contractions.

Nitrous oxide is not as widely used as parenteral opioids or neuraxial methods of labour analgesia. It appears to be a part of the Finnish regimen for labour analgesia, however, with approximately half of women using it during labour (National Institute for Health and Welfare 2008), while 80.5% of women use nitrous oxide during labour in Sweden (Waldenström & Irestedt 2006). Other

countries which widely use nitrous oxide in labour include the United Kingdom, Canada, Australia, and New Zealand (Rosen 2002).

2.4 Reduction of pain in obstetric analgesia

2.4.1 Nature and assessment of labour pain

Labour pain appears to be forgotten to some extent over a period of time. In repeated interviews, it was noted that mothers initially assessed their overall pain scores (VAS 0–150 mm) as 72.5% of the total length of the 'linear analogue' immediately after delivery when a systemic opioid analgesia with optional inhalation of either nitrous oxide or methoxyflurane had been used, but this decreased over three months to less than 60%. A similar decrease over time in the reported scores was observed in mothers receiving epidural analgesia, albeit at a lower level (Robinson *et al.* 1980). Probably the longest follow-up study on the recollection of labour pain in a large Swedish cohort suggested that, while there is a tendency for the memory of the pain to decrease in general, a minority of parturients (16%) remembered the pain as more painful at 5 years than at 2 months after delivery (Waldenstöm & Schytt 2009). In an interim analysis of this follow-up at 1 year, it was noted that – in contrast to the observation by Robinson *et al.* (1980) - EDA was associated with a difficulty in forgetting the pain (Waldenström & Irestedt 2006) while nitrous oxide was not. The paper could not exclude a selection bias, but suggests several possible mechanisms for the difference observed.

While the physiologic and transient nature of labour pain may be true for the majority of mothers, there may be a proportion of mothers in which the painful experience results in prolonged suffering including subsequent infertility (Gottvall & Waldenström 2002) and post-traumatic stress disorders (Ballard *et al.* 1995). The risk of postnatal depression also appears to be higher among those who have had no pain relief at all compared to those with effective analgesia (Hiltunen *et al.* 2004). This is a result from an observational study, however, and does not prove causality.

Pain measurement is essential in evaluating the relative effectiveness of different therapies. Early experiments studying labour pain included the use of a dolorimeter which was a device which produced a painful stimulus of 3 seconds duration to the skin. This experimental pain was applied during or after the

contraction and the parturient noted when the pain was similar in intensity. The pain scale was 0–10.5 dols where the 1 dol is a unit of pain equal to one-tenth of the greatest painfulness. Ten dols were equal to a third-degree burn of the skin. With this method, it was noted that pain increases during labour from 3–4 dols during early labour up to 8–10 dols at the transition from the 1st to the 2nd stage of labour. During the 2nd stage the maximum of 10 dols was reached after which the method was incapable of establishing whether or not pain increased any further. (Javert & Hardy 1950)

Subsequent to this, the subjective nature of pain has been acknowledged and various pain scoring systems have been developed in which the researcher relies upon subjective reporting by the person in pain. Labour pain is measured by asking the parturient to quantify the pain on one or several pain scores. One-dimensional pain scales include verbal rating scale (VRS), visual analogue scale (VAS), 11-Box-plot and numerical rating scale (NRS). In most clinical studies concerning labour analgesia, the parturient assesses the pain of uterine contractions during a certain period of time or the whole 1st or 2nd stage, or gives one single score for the whole duration of labour. Obviously, the best resolution in labour pain measurement is obtained by asking the parturient to grade the pain after every uterine contraction. The McGill Pain Questionnaire (MPQ) is an example of a multidimensional pain scales. This employs 20 sets of words describing the sensory, affective and evaluative dimensions of the experience of pain. Labour pain was characterised by 141 Canadian women Using the MPQ as horrible or excruciating by 25% of parturients at a cervical dilatation < 5 cm whereas the same words apply to labour pain in 46% after a cervical dilatation of 5 cm. It was also noted that primiparae scored higher pain rating indices than did multiparae. There was a large variation in the scores with both groups of parturients, however, ranging from nearly no pain at all to the highest possible scores. In general, the parturients' scores were of the highest that have been noted with MPQ in various pain states (Melzak *et al.* 1981, Melzack *et al.* 1984).

A number of factors have been identified which modify pain including mother's age, ratio of usual weight to height and sociocultural status as well as parity, tendency for dysmenorrhoea, back pain during menstruation and labouring position (vertical vs. horizontal) (Lowe 2002). Prior antenatal classes and the presence of a support person have been noted as factors which are associated with lower pain ratings (Melzack *et al.* 1984).

Pain relief can be measured as the difference of the pain score before any analgesic is given and the pain score during the effect of the intervention. This has

been termed as the pain intensity difference (PID) (McQuay & Moore 1998). The progressive pattern of pain in labour is a challenge when the PID is calculated. For example, Morley-Forster *et al.* (2000) noted that mean pain scores (VAS 0–100 mm) were 65 and 67 mm in groups receiving fentanyl and alfentanil, respectively via IVPCA, before the initiation of medications. During the treatment, the average pain scores were 65 and 86 mm ($p < 0.01$) at a 7 to 10 cm dilatation of the uterine cervix. If the baseline figures had been used for calculation of PID, one would have concluded that there was little or even a worsening effect on pain. However, most of the mothers rated the pain relief as good or adequate. When methods of analgesia are compared, the increasing pattern of labour pain can be taken into account by designing a cross-over study with repeated changes in the medication (Yeo *et al.* 2007). In parallel studies, labour pain comparisons should be made between groups at similar phases of progress in labour.

A variant of the VRS is the pain relief scale which employs 5 ranked categories (none, slight, moderate, lots, complete). This is an essential part of the Oxford pain chart which is used to compare analgesic efficacy of drugs (McQuay & Moore 1998). A pain relief scale provides a shortcut from pain to assessing the analgesic effect due to the fact that patients have the same baseline of no relief even if they had different pain intensity before the start of analgesic medication.

It has been suggested that pain relief score is more sensitive than PID. Although studies using both the analogue pain intensity scale and the verbal relief scales usually show good correlation between these methods of measuring analgesia, in situations with very severe initial visceral pain a lower correlation has been noted with a proportion of patients reporting little decrease in pain scores but substantial pain relief (Littman *et al.* 1985). In labour pain, in two studies concerning sevoflurane analgesia, significant changes in pain relief scores were noted with no consistent change in pain intensity or feeling of well-being (Yeo *et al.* 2007). One could speculate that a unidimensional pain score is too insensitive to reveal changes in both the affective and evaluative dimensions of pain as well as the sensory one, and whether there might have been changes in the respective parts of the MPQ. While little change in VAS for pain intensity was observed after giving morphine or pethidine to parturients, less tension and discomfort and more calmness was noted indicating a possible change in the affective dimensions of the pain (Olofsson *et al.* 1996 a,b). A suspicion has been expressed, however, as to whether these psychological effects could be termed as ‘true analgesia’ if there is no reduction in the pain scores (Olofsson *et al.* 1996b).

To date, it is unclear how large a decrease in labour pain would be clinically significant. Moreover, it is not known what amount of labour pain would be acceptable or optimal during the different phases of labour. As we do not know the exact purpose of labour pain, it is not possible to set a defined goal as to by what amount pain should be reduced. We do have some clues, however, as to what women want. According to an antenatal questionnaire, the pain threshold at which the women would opt for pain relief varies a great deal. While approximately 18 % of women would like to have some form of analgesia with mild or moderate pain 19% would accept pain relief only if the pain were intolerable. The majority of women would like to wait until pain becomes severe or very severe (Ranta *et al.* 1995). The parturients choosing to deliver via "natural childbirth" are not different from this majority in terms of the threshold for asking for analgesia. Those who eventually opt for EDA have an average pain intensity score of 7 on a scale of 0–10 during the latent phase of labour, whereas those who managed to deliver without an epidural reported a lower pain score (Kannan *et al.* 2001). During labour analgesia with an epidural block the median pain score among those who required additional medication was 4 with a range of 2–10 and 93% of women with a NRS > 3 wanted more medication (Beilin *et al.* 2000, Beilin *et al.* 2003).

Todd *et al.* (1996) and Gallagher *et al.* (2001) concluded that a 13 mm change in a 100 mm scale would represent a clinically significant measure which would reflect a change to a little less or a little more pain derived from repetitive self-assessments of pain in emergency departments among patients most - if not all - of whom were non-pregnant. In another context, the difference of 1.7 points in a NRS of 0–10 has been found to represent a clinically significant reduction in chronic pain (Farrar *et al.* 2001) and a 33% reduction at the NRS or pain relief of 2 on a scale of 0–4 in a more acute, cancer breakthrough pain. In the latter case, resorting to an additional rescue dose in a clinical study was used as the cut-off point for clinical significance (Farrar *et al.* 2000). It was suggested that the type of rescue medicine would have an effect on the pain level at which a top-up is requested as the patient considers not only the pain that can be tolerated but also the possible side effects that will come with the rescue medicine. This suggestion is supported by the fact that in labour pain, Jain *et al.* (2003) noted that significantly more (67%) women request a top-up when the pain score was less than 7 during EDA compared with opioid analgesia (30% and 31.8% with pethidine and tramadol, respectively) which is probably associated with an increased risk of side effects as compared to EDA. Another possible explanation

for this difference observed by Jain *et al.* (2003) is that women using an opioid analgesia find it easier to stand a stronger pain than those with EDA.

Recently, efforts have been made to quantify pain objectively. Functional MRI has been employed to identify the locus where the blood-oxygen-level-dependent (BOLD) signal caused by somatic pain is reduced by an administration of systemic analgesic medication (Wise *et al.* 2004). The activation of localised μ-receptor activated systems has been observed with positron emission tomography (PET) -scans using a μ-receptor-specific radiotracer. The sensory and affective pain dimensions distinguished by MPQ were noted to be linked with different sites of activity in the brain (Zubieta *et al.* 2001). Another way to quantify nociception is the surgical stress index (Ahonen *et al.* 2007, Huiku *et al.* 2007). None of these methods, however, are currently applicable in labour pain.

Good pain relief has traditionally been thought to be one of the key determinants of patient satisfaction among parturients. An inquiry among 1000 mothers in London revealed, however, that most satisfied women were those who did not use any pain relieving medication during labour (Morgan *et al.* 1982). Maternal satisfaction with the experience of childbirth is a complex issue in which pain relief or lack of it may have an important role in some cases. Hodnett (2002) noted, however, that pain relief is not high on the list of priorities in general in a systematic review of 29 observational studies, 7 randomised controlled trials (RCT) and 5 systematic reviews in which childbirth satisfaction was an outcome variable with special emphasis on pain management, including mothers from different cultures over almost 30 years. With respect to women's evaluations of their childbirth experiences, the most important factors are whether the parturient feels that the care-givers are helpful and whether she feels that she has an active say in decision making. Pain and pain relief have a role in the childbirth experience when the parturient's experience is in conflict with her expectations of either of these. In contrast to the results of the review by Hodnett, however, a Swedish study with a focus on the proportion of mothers who had the most negative childbirth experience found that having experienced the "worst imaginable" pain was one of the two strongest predictors of a negative overall experience of childbirth (Waldenstöm *et al.* 2004).

The concept of satisfaction with labour analgesia may not be a straightforward assumption of equality between analgesic potency and satisfaction with a given method of analgesia. Availability or non-availability of the method or delay in receiving it may also play a role (Robinson *et al.* 1998). In this respect, systemic opioids and nitrous oxide have an advantage over EDA

because they can be given by the midwife without the delay or non-availability caused by changes in the availability of the anaesthetists. When analgesia – in terms of reduction in pain scores – is equally efficient between two methods, factors such as rapid onset and a lesser motor block appear to make a difference in satisfaction with labour analgesia (Collis *et al.* 1995). It seems that - as with the memory of pain over time - the mothers' assessment of the satisfaction with the analgesia tends to change over time. Howell *et al.* (2001) noted a shift from "reasonably satisfied" towards "completely satisfied" over 12 months. Maternal satisfaction with labour analgesia has been assessed with direct questioning using a VAS or VRS for satisfaction or by asking the parturients to give a pain relief score after the delivery. Abboud *et al.* (1981), Philipsen & Jensen (1990), Sharma *et al.* (1997) and Jain *et al.* (2003) used the question of whether the patient would have the same agent again as an indirect proxy to patient satisfaction.

Although the term PCA implies some degree of subjective control over the process of analgesia the perceived feeling of control has not been confirmed by research (Chumbley *et al.* 1998). Introduction of the PCA principle in the EDA did not increase the feeling of being in control of analgesia or increase satisfaction with analgesia in the study by Nikkola *et al.* (2006).

2.4.2 Analgesia with remifentanil, epidural block and nitrous oxide

A number of studies have been published to date describing how systemic remifentanil relieves pain during labour (table 1). If the VAS expressed in millimetres is divided by 10 (making a uniform score of 0–10) and a similarity between NRS and VAS is assumed, there seems to be a fast action with reduction of pain by -0.3 to 5.4 (mean or median, depending on the original study) during the first hour of remifentanil analgesia. The slightly negative PID was observed in a setting with a fast, fixed PCA-bolus of 40 µg/kg without a background infusion (Blair *et al.* 2005) while the largest PID was noted in a study employing a flexible PCA-bolus of 0.27–0.93µg/kg (Evron *et al.* 2005). Unfortunately, the duration of the bolus was not reported in the latter study. Four studies have quantified pain during the entire duration of the 1st stage of labour and their findings indicate that pain relief is sustained during remifentanil analgesia. The overall pain scores for the first stage of labour tend to be somewhat higher than those reported for the first hour of analgesia (table 1). Four studies have compared remifentanil with pethidine displaying a somewhat better analgesia with remifentanil (table 1). Blair *et al.* (2005) did not observe a significant difference in pain scores between

remifentanil and pethidine analgesia, however, in spite of an observable difference in overall satisfaction in favour of remifentanil.

An alternative method of comparing the efficacy of pain relief provided by different methods of analgesia includes counting failure rates. Table 3 lists the proportion of parturients receiving remifentanil analgesia which has subsequently been terminated and replaced with EDA. This could serve as a proxy to failure rate. It seems apparent that the there is little association between PID and the rate for resorting to EDA as the two papers reporting opposing findings as to the effect on pain score reported nearly the same percentage for converting to EDA (10% in the study by Blair *et al.* (2005) vs. 10.8% as reported by Evron *et al.* (2005)).

Lumbar epidural block is regarded as the golden standard for modern labour analgesia. Its good record of effectiveness was reported as early as 1957 by one of the pioneers, John Bonica, who reported 189 cases out of which only 1.6% were considered as having worked poorly. No effort was made to quantify the pain, however, and it is not clear who classified the results of analgesia (Bonica *et al.* 1957). The superiority of EDA in comparison with systemic opioid analgesia is well established in a number of RCTs (table 2). There seems to be a steep fall in pain scores (0–10) from 7.1–7.9 to 0–4 during the first hour (Thorp *et al.* 1993, Bofill *et al.* 1997, Jain *et al.* 2003) with a sustained effect throughout the 1st stage of labour. Most studies compared EDA with systemic pethidine which has been thought to provide near to no analgesia at all in labour pain (Olofsson *et al.* 1996b, Ranta *et al.* 1994). A decrease of pain by 0–4 with systemic opioid analgesia from a baseline pain score of 6.9–9 on a scale of 0–10 has been noted, however, in several large studies (Thorp *et al.* 1993, Ramin *et al.* 1995, Sharma *et al.* 1997, Bofill *et al.* 1997, Sharma *et al.* 2002, Jain *et al.* 2003) (table 2). In a systematic review, Leighton & Halpern (2002) calculated a weighted mean difference of 40 mm in favour of EDA for the 1st stage of labour ($p < 0.0001$). Halpern *et al.* (2004) noted a comparable difference between PID achieved with EDA and with opioid analgesia when the opioid used in the control group was fentanyl. With respect to patient satisfaction with the analgesia, EDA has consistently ranked better than systemic opioid analgesia (Leighton & Halpern 2002). Jain *et al.* (2003) pointed out, however, that while mothers using systemic opioid analgesia did not consider the pain relief excellent as often as those using EDA, a considerable proportion rated it as very good or good. In RCTs comparing epidural with opioid analgesia, a larger proportion (73–95%) of mothers in the epidural groups stated that they

Table 1. Pain, pain relief scores, and doses during remifentanil analgesia in labour. N = total number of patients in the study, RCT = randomised controlled trial, R = remifentanil, P = pethidine, VI = Variable infusion, VB = Variable bolus, Contl = continuous infusion. Data are mean or median for the scores and consumption, for categories: n = number, % = proportion.

Study / N	Type of study	Pain scores baseline	Pain scores 1st hour	Pain scores 1st stage	Satisfaction with analgesia	Method of assessment	Remifentanil doses	Control agent	Remifentanil consumption
Olufolabi *et al.* 2000 N=4	Open study	3	2–3	–	–	VRS 1–4:	0.25–0.5 µg/kg bolus	–	Approximately 0.05 µg/kg/min for the 1st hour#
Blair *et al.* 2001 N=21	Open study	8	5–6	5–6[a]	8 with the higher dose	VAS (0–10) every 15 minutes until the individual effective dose	IVPCA 0.25–0.5 µg/kg bolus, dose escalation, lock-out time 2 minutes	–	–
Volikas & Male 2001 N=17	Double blind RCT			–	–	VAS (0–100 mm) hourly	IVPCA 0.5 µg/kg bolus, lock-out 2 minutes[b]	Pethidine IVPCA	–
R=9		R 47#	R 28#						
P=8		P 46#	P 52#						
Thurlow *et al.* 2002 N=36	RCT			–	Very good or excellent (on a 5-step scale)	VAS (0–100mm) every 30 minutes for 2 hours	IVPCA 0.20 µg/kg lock-out 3 minutes	Pethidine IM + antiemetic	–
R=18		R 71	R 48		R 9				
P=18		P 68	P 72		P 1 (p<0.002)				
Volikas *et al.* 2005 N=50	Open study	69	33 #	46[a]	–	VAS (0–100mm) hourly	IVPCA 0.5 µg/kg bolus, lock-out 2 minutes + antiemetic	–	0.12 µg/kg/min
Blair *et al.* 2005 N=39	RCT					VAS (0–10 cm) every 30 minutes	IVPCA 40 µg bolus, lock-out 2 minutes	Pethidine IVPCA	–
R=20		R 7#	R 7.3#	R 6.4*	R 8				
P=19		P 6#	P 8#	P 6.9*	P 6 (p=0.001)				
Evron *et al.* 2005 N=88	Double blinded RCT				(1–4):	VAS (0–100 mm) for pain at baseline, 1 hour, end of the 1st stage	IVPCA 0.27–0.93 µg/kg bolus, dose escalation, lock-out 3 minutes	Pethidine	0.06 µg/kg/min
R=43		R 86	R 36	R 32.6	R 3.9				
P=45		P 88	P 59 (p<0.001)	P 53.5 (p<0.001)	P 1.9 (p<0.001)				

Study / N	Type of study	Pain scores baseline	Pain scores 1st hour	Pain scores 1st stage	Satisfaction with analgesia	Method of assessment	Remifentanil doses	Control agent	Remifentanil consumption
Balki *et al.* 2007 N=20	Double blinded RCT	VI 7.7 VB 7.8	VI 3.8# VB 5.6#	VI 6.1 VB 5.5	VI 8.2 VB 8.0	NRS (0–10) every 30 minutes	IVPCA VI: 0.25 µg/kg bolus, infusion 0.025–0.1 µg/kg/min	IVPCA VB: 0.25–1 µg/kg bolus, infusion 0.025 µg/kg/min	0.09 µg/kg/min
Balcioglu *et al.* 2007 N=60	Systematically RCT	10 in both groups#	< 3 in both groups#	< 3 in both groups#	VRS (1-5): excellent: 46% for both groups	VAS (0–10) 5-15 minutes intervals until 90 minutes	IVPCA 0.15 µg/kg bolus infusion 0.1 µg/kg/min	Same bolus, infusion 0.15 µg/kg/min	0.25–0.27 µg/kg/min
Evron *et al.* 2008 N=213	RCT blinded for the operator	All groups <30	–	R 49[a] EDA and R+EDA 27[a] (p<0.001)	–	VAS (0–100 mm)	IVPCA bolus 20 µg, lockout 3 minutes, background infusion 0.025µg/kg/min	EDA	R 0.14 µg/kg/min R+EDA 0.07 µg/kg/min
Hodgkinson & Hughes 2008 N=612	Audit	–	–	No pain or bearable pain: 77.3%	Satisfied or very satisfied: 85%	–	–	–	–
Harbers *et al.* 2008 N=305	Open study	8.5	5.8	–	–	VAS	IVPCA bolus 25 µg/kg, lock-out 3 minutes, background infusion 80–120 µg/h	–	–
D'Onofrio *et al.* 2009 N=205	Open study	9.4	3.6	–	Satisfied or very satisfied (n): 179	VAS (0–10)	ContI 0.025–0.15 µg/kg/min	–	Maximum infusion rate median 0.075 µg/kg/min
Foley & Hill 2009 N=10816 R=1374	Audit of regional database	–	–	–	–	–	–	–	–
Tveit &Rosland 2009 N=41	Open study	7.6#	5.0#	–	92.5% satisfied with analgesia	VAS (0–10)	IVPCA bolus 0.15–1.05 µg/kg, lock-out 2 minutes. Bolus duration 1 minute	–	–

Approximated from figure

[a] Given for entire labour

[b] Bolus duration 18 s (information provided by the author via e-mail)

would opt for a similar analgesia in any future labour compared with 30–70% of the women in the opioid groups (table 2). In a nonrandomised study, Ranta *et al.* (1994) noted that no mothers (0 out of 82) assessed their EDA analgesia as being poor (three category VRS: good, moderate, poor) on the third day after delivery compared with all other methods included in the study (water blocks 15%, nitrous oxide 28%, pethidine 17%, paracervical block 15%).

While epidural analgesia provides effective pain relief in general, it will sometimes not work at all or work poorly. These problems are reflected in the re-site rate which depends on the actual method and the equipment. A very low failure rate of 0.5–0.8% was reported by Norris *et al.* (2001) in a randomised prospective study including 2183 parturients receiving either CSE or EDA, with no difference between the two methods. In another setting, in a large retrospective study including 3233 vaginal deliveries the epidural replacement rate was 12.1% (Eappen *et al.* 1998). If more precise criteria are applied on whether the epidural fails, a higher incidence is noted. Beilin *et al.* (2000) reported failure rates of 36% and 19% when the epidural space had been identified with loss of resistance with air or saline, respectively. The block was classified as a failure if the parturient required additional medication to treat the pain 25 minutes after the test dose of 3 ml of 0.25% bupivacaine after which 10 ml of the same solution was injected in two divided doses. Median pain scores were still low (1 and 2 on a scale of 0–10), however, at 15 minutes after initiation of the main epidural bolus in groups using loss of resistance (LOR) with saline or air, respectively.

It is controversial whether nitrous oxide provides labour pain relief. Klikowitsch (1881) noted that parturients stopped crying and expressed pain relief during labour when nitrous oxide was employed. In a systematic review, Rosen (2002) concluded that despite the use of nitrous oxide for more than 100 years in obstetrics we are not any closer to quantifying nitrous oxide's analgesic effects in labour. He came to this conclusion after reviewing 11 studies with conflicting results. The most convincing papers have also arrived at conflicting conclusions. There was a dose-effect relationship when nitrous oxide was administered intermittently (Westling *et al.* 1992) with the best analgesia experienced when the gas was applied continuously in a randomised, partly-blinded, cross-over study. Opposed to this finding, there was no evidence of analgesic effect in a double-blind cross-over study by Carstoniu *et al.* (1994) in which compressed air was used as a placebo during one of the two study periods including five uterine contractions. Another systematic review came to the conclusion that inhaled nitrous oxide has analgesic efficacy for relief of labour pain (Kronberg &

Thompson 2005). Among the papers included in the review, Kronberg & Thompson based the conclusion on a study by McAneny *et al.* (1963) with a dose-effect relationship observed between 50%, 60% and 70% nitrous oxide concentrations with a ceiling effect at 70%. The Committee report concerning 799 mothers using either 50% or 70% nitrous oxide, however, failed to find any difference in the analgesic effect between the two concentrations (Committee on Nitrous Oxide and Oxygen Analgesia in Midwifery 1970). The writers of the latter paper admitted that the questionnaire referred to "help" rather than the degree of pain relief obtained. In addition, the mothers answered the questions as late as the 3rd day after delivery. The relatively long period between labour and the study may have diluted their recall. Both these old British studies allowed the free use of injection of analgesics. These were used frequently suggesting an incomplete analgesic effect for nitrous oxide. The Committee report did not include any information as to which proportion of the parturients received additional tranquilizers or narcotics, but noted that this was not influenced by the concentration of nitrous oxide. McAneny *et al.* (1963) reported 22%–42% of the parturients receiving more than one injection of analgesics. Hence, at least part of the reported pain relief could have been due to the effect of the adjuvant medication.

Asking whether the parturient would continue using the method after the trial has revealed that a majority of parturients probably feel they benefit from inhaling nitrous oxide. Bergsjø & Lindbaek (1971) reported that 33 out of 40 parturients continued using nitrous oxide after a cross-over trial during which nitrous oxide and methoxyflurane were used during 3 contractions with a wash-out period lasting for 1 contraction. Comparable results were obtained by Abboud *et al.* (1981) after the 2nd stage analgesia with 86% of mothers in the groups receiving nitrous oxide answering "yes" to the question of whether the patient would have the same agent again.

Table 2. Variables related to pain in randomised controlled trials comparing epidural analgesia (EDA) with systemic opioids (Opi). N = total number of patients in the study, CSE = combined spinal epidural, PCEA = Patient controlled epidural analgesia, Data are mean or median for continuous variables and n (= number of events) or % for dichotomous variables.

Study / N	Pain scores baseline	Pain scores 1 hour post analgesia	Pain scores during 1st stage	Satisfaction with analgesia	Cross-over n/N or %	Protocol	Comments
Robinson *et al.* 1980 N=93	–	–	EDA 37.5% Opi 61.6% (p<0.001)	EDA 88.1% Opi 66.3% (p<0.001)	Only those adhering to protocol included in the analyses	EDA Bupivacaine 0.5% 5-10 ml + top-ups as required Vs. IM Pethidine + inhalation analgesia as required[a]	% of VAS 0-150 mm Discomfort rating 1st stage Epidural 37.0% Opioid 41.2%
Philipsen & Jensen 1990 N=97	–	–	EDA 11 Opi 65 (p<0.001)	EDA 73% [b] Opi 30% [b] (p<0.001)	–	EDA Bupivacaine 0.375% 1 ml / 10 kg Vs. IM Pethidine	VAS 0-100 mm 2nd stage pain relief by pudendal block in both groups
Thorp *et al.* 1993 N=93	EDA 8[#] Opi 8[#]	EDA 2.4 Opi 7.0	EDA 2.9[#] Opi 7.9[#]	–	Opi to EDA: 1/45	EDA 0.25% bupivacaine bolus + 0.125% infusion Vs. IV Pethidine[a]	VAS 0-10
Ramin *et al.*1995 N= 1330	EDA 9 Opi 9	–	EDA 3 Opi 8 (p<0.001)	EDA 60% [c] Opi 22% [c] (p<0.05)	Opi to EDA: 103 / 437 (24%)	EDA bupivacaine 0.25% bolus + 0.125% infusion w/ fentanyl 2 µg /ml Vs. IV Pethidine[a]	VAS 0-10 Hypotension (<100 mmHg) in 22% with EDA

Study / N	Pain scores baseline	Pain scores 1 hour post analgesia	Pain scores during 1st stage	Satisfaction with analgesia	Cross-over n/N or %	Protocol	Comments
Sharma *et al.*1997 N=358	EDA 9# Opi 9#	–	EDA 3 # Opi 5#	EDA 95% b 90%d Opi 70%b 65% d (P<0.001)b, d	Opi to EDA 5/ 259 (2%)	EDA Bupivacaine 0.25% bolus + 0.125% infusion w/ fentanyl 2 µg /ml Vs. IVPCA pethidine[a]	VAS 0-10 cm Maternal hypotension: EDA 31%, Opi 0 (p<0.0001) Naloxone, neonate: EDA 1%, Opi 5% (p<0.05)
Nikkola *et al.*1997 N=20	–	–	–	EDA 80% e Opi 60%e	Opi to EDA: 4/10 (40%)	EDA Bupivacaine 0.5% boluses Vs. IVPCA Fentanyl	More tiredness and dizziness in opioid group No difference in Apgar- and Amiel Tison's Neurological Capacity -scores Opi neonates' SaO_2 lower
Bofill *et al.* 1997 N=100	EDA 7.1# Opi 6.9#	EDA 4.4# Opi 6.5#	–	–	Opi to EDA: 12/51 (24%)	EDA Bupivacaine 0.25% bolus + 0.125% infusion w/ fentanyl 1.5 µg/ml Vs. IV butorphanol 1-2[a]	VAS 0–10 cm Opi 1 neonate received naloxone
Clark *et al.*1998 N=318	–	–	–	–	Opi to EDA: 84/ 162 (52%) EDA to Opi: 5/156 (3%)	EDA Bupivacaine 0.25% 9 ml + 0.125% infusion w/ fentanyl 1 µg/ml Vs. IV Pethidine	UApH <7.15: EDA 13/147 (8.8%) Opi 21 / 78 (26.9%) (p<0.05)

Study / N	Pain scores baseline	Pain scores 1 hour post analgesia	Pain scores during 1st stage	Satisfaction with analgesia	Cross-over n/N or %	Protocol	Comments
Gambling *et al.* 1998 N = 1223	CSE 10	CSE 0	–	CSE 82%#[c] Opi 35 %#[c]	Opi to EDA 102 /607 (17%)	CSE sufentanil 10μg + Epidural Bupivacaine 0.25% bolus + 0.125% infusion w/ fentanyl 2 μg/ml Vs. IV Pethidine[a]	VAS 0–10cm More emergency CS due to FHR changes in the CSE group
Loughnan *et al.* 2000 N=614	–	–	–	EDA 88%[f] Opi 50%[f]	Additional analgesia: EDA l0% Opi 40%	EDA Bupivacaine 0.25% bolus + 0.125% infusion Vs. IM Pethidine	
Howell *et al.* 2001 N=338	–	–	–	EDA 58% [g] Opi 48%[g]	–	EDA bupivacaine 0.25% bolus + top-up doses by midwife Vs. IM Pethidine	Primary outcome was back pain
Lucas *et al.* 2001 N=738	–	–	–	EDA 54% [h] Opi: 19% [h] (p<0.001)	Additional analgesia: EDA 3 (0.8%) Opi 3 (0.8%)	EDA bupivacaine 0.25% bolus + infusion 0.125% w/ fentanyl 2 μg/ml Vs. IVPCA Pethidine [a]	Pregnancy-induced hypertension Hypotension: EDA 11%, Opi 0% (p<0.001) Naloxone, neonate: EDA 1%, Opi 12% (p<0.001)
Sharma *et al.* 2002 N=494	9 in both groups	–	PCEA 3 Opi 5	PCEA 95% [h] Opi 69%[h] (p<0.001)	Opi to PCEA 14/223 (6%)	PCEA Bupivacaine 0.25% bolus + 0.0625% infusion+boluses w/ fentanyl 2μg/ml Vs. IVPCA Pethidine [a]	VAS 0–10 1-minute Apgar scores lower and $UApCO_2$ higher in the pethidine group. Naloxone, neonate: PCEA 0, Opi 6 % (p<0.001)

Study / N	Pain scores baseline	Pain scores 1 hour post analgesia	Pain scores during 1st stage	Satisfaction with analgesia	Cross-over n/N or %	Protocol	Comments
Head *et al.* 2002 N=116			EDA 4 Opi 7 (p<0.001)[j]	EDA 3 [h] Opi 2 [h] (p=0.002)	Opi to EDA 1/60 (2%)	EDA Bupivacaine 0.25% bolus+ 0.125% infusion w/ fentanyl 2 μg/ml Vs. IVPCA pethidine [a]	Severe preeclampsia VAS 0-10 Hypotension: EDA 9%, Opi 0% (p=0.02) Naloxone, neonate: EDA 9%, Opi 54% (p<0.001)
Jain *et al.* 2003 N=128	7.2 all groups[#]	EDA O[#] Opi 5.2[#]	–	EDA 81.4% [b] 77% [c] Opi 46.1–47.7% [b] 13–15% [c]	–	EDA Bupivacaine 0.15% w/ fentanyl 3 μg/ml boluses (or infusion) Vs. IM Pethidine Vs. IM Tramadol	VAS 0–10 More maternal sedation and neonatal respiratory problems in opioid groups More urinary retention in epidural group RR<8 by none
Halpern *et al.* 2004 N=242	PCEA 80 Opi 90		PCEA 20 [i] Opi 60 [i] (p<0.0001)	PCEA 7.7 Opi 6.8 (p=0.02)		PCEA Bupivacaine 0.1% w/ 100 μg fentanyl + bupivacaine 0.08% + fentanyl 1.6 μg/ ml Vs. IVPCA fentanyl	VAS 0-100mm and 0-10 Naloxone, neonate: PCEA 3%, Opi 17% (p<0.001) Apgar (1 min) <7: PCEA 17%, Opioid 28% (p=0.04)

[#] Pain scores approximated from figure(s)

[a] + antiemetic

[b] Would choose the same analgesia in next delivery

[c] Excellent or very good in mother's assessment with 5-point descriptive scale (excellent, very good, good, fair and poor) after delivery

[d] Excellent, very good or good analgesia in mother's assessment with 5-point descriptive scale (excellent, very good, good, fair and poor) after delivery

[e] Excellent or good in mother's assessment next day with 4-point descriptive scale (excellent, good, moderate and poor)

[f] Excellent or good in mother's assessment 24 after delivery with 5-point descriptive scale (excellent, good, satisfactory, poor or very poor)

[g] Completely satisfied

[h] Excellent (Lucas *et al.* 2001), excellent or good (Sharme *et al.* 2002) or median (Head *et al.* 2002) in mother's assessment after delivery with 4 point scale (excellent [4], good [3], fair [2], poor [1])

[i] Mean of hourly (incl. 2nd stage) assessments

[j] Error in the original paper. Corrected according to data provided by the author.

2.5 Side effects

2.5.1 Respiratory effects

In pregnancy, an increase in resting minute ventilation has been observed as early as at 8 weeks of gestation. The change occurs primarily in the tidal volume resulting in low carbon dioxide content in arterial blood while there is little or no change in the respiratory rate. At term, minute ventilation is 30–50% above non-pregnant values (Crapo 1996). In terms of oxygenation the increase in ventilation may be partially offset by decreased efficiency in gas transfer (Milne 1979). Nevertheless, SaO_2 is high as noted by Kinsella & Thurlow (2000) when they studied 100 women during the 3rd trimester of pregnancy finding that the saturation values (median 98%, range 95–100%) were not different from those measured in the non-pregnant. In late pregnancy, functional residual capacity is smaller compared with the non-pregnant state and the consumption of oxygen increased resulting in a rapid reduction in arterial oxygen content in case of reduction of ventilatory drive or apnoea. During labour, the fluctuation of respiratory drive caused by labour pain results in inconsistent patterns of breathing including periods of hyperventilation followed by low tidal volumes, bradypnoea and short periods of apnoea. These result in desaturation in a proportion of parturients. Although opioids have the potential for respiratory depression, it is controversial to which extent their use during labour causes hypercapnia and hypoxaemia or whether the desaturations seen during labour are caused by pain.

Minnich *et al.* (1990) observed 15 labouring women using pulse oximeter and end tidal carbon dioxide ($ETCO_2$) monitoring with a nasal catheter, as well as the continuous monitoring of uterine contractions. They noted periods of desaturation in 10 parturients, out of whom 7 had received opioid analgesics intravenously (butorphanol 1–2 mg or pethidine 50 mg). After the institution of EDA, the tendency for hypoxaemia resolved and a normal capnogram was observed. The writers concluded that decreases in SaO_2 were caused by pain which was followed by apnoeic periods, with a close correlation between perceived pain during the uterine contractions and the consequent decrease in SaO_2. Similarly, Deckardt *et al.* (1987) noted that epidural top-up doses of 4 ml of bupivacaine 0.25% were followed by a levelling of the decreases in SaO_2 during labour. They also found a significant difference in saturation between parturients with an epidural block (mean SaO_2 94.3%, range 85–100%) and those labouring with

intramuscular pethidine 50–100 mg and nitrous oxide (mean 88.8%, range 74–100%). In a larger study with 474 parturients, desaturation periods to < 91% lasting for 10 seconds – 10 minutes were observed during labour in 85 parturients (Porter *et al.* 1992). The parturients with desaturations also had a lower mean SaO_2 during the 1st stage of labour than those who did not have desaturation periods. Desaturations were noted in 8% of those labouring without any opioids or sedatives. If the woman received pethidine or butorphanol she had a relative risk of 3.4–4.5 to desaturation. The writers suggested that respiratory depression following the exposure to narcotic analgesics could have been the reason for the desaturation. Due to the study design, however, a selection bias cannot be excluded. Other risk factors included young age and nulliparity.

Remifentanil has a strong potential for respiratory depression causing a dose dependent increase in the expiratory time and correspondingly a decrease in respiratory rate. Inspiratory time increases only with a larger target controlled infusion (TCI) (1.5 ng/ml). The tidal volume decreases more with low target (0.7 ng/ml) compared to larger infusions (1.1 and 1.5 ng/ml). (Mitsis *et al.* 2009) Babenco *et al.* (2000) noted a significant ventilatory depression, which started at 30 seconds and peaked at 2.5 minutes when a bolus of 0.5 μg/kg was given as a fast injection over 5 seconds, and had an effect on ventilation during the subsequent 20 minutes. Hypoxaemia has been noted in many studies concerning remifentanil labour analgesia (table 3). Remifentanil analgesia was not different from pethidine in three comparative studies (Volikas *et al.* 2001, Thurlow *et al.* 2002, Blair *et al.* 2005), but 50% nitrous oxide in oxygen was used by a large proportion of the parturients in all three of these studies. In a study without the potentially interfering effect of inhaled nitrous oxide in oxygen, Evron *et al.* (2005) noted a better SaO_2 with remifentanil at all time points (after 1 hour of analgesia, at the end of the 1st and 2nd stages of labour). Oxygen supplementation appears to reduce hypoxemic events, but in the report by Hodgkinson & Hughes (2008), remifentanil analgesia was terminated in 5 out of 612 cases due to hypoxaemia refractory to supplemental oxygen.

EDA seems to normalise the hyperventilation–hypoventilation cycle and resolves the desaturation periods by alleviating contraction pain. In a nonrandomised trial, however, Arfeen *et al.* (1994) noted at least one desaturation < 90% lasting for more than 12 seconds during a short observation period of 23 – 38 minutes in 33% of the parturients with 0.1% plain bupivacaine given epidurally. In contrast to this finding, an observational study by Griffin *et al.* (1995) reported that EDA with local anaesthetic was associated with only

negligible hypoxaemia. Parturients with EDA including fentanyl in the epidural solution were, however, at risk of respiratory depression. Porter *et al.* (1996) noted a relatively large proportion (approximately 35%) of parturients with EDA demonstrating desaturations to < 95%. There was no difference in the percentage of parturients with desaturation < 95% for ≥ 1 minute when EDA with epidural opioid was compared with EDA of bupivacaine alone during the 1st stage of labour, but more desaturations were noted with epidural fentanyl in the 2nd stage of labour. Surprisingly, only three RCTs comparing EDA with systemic opioid analgesia (table 2) have employed the measurement of SaO_2 or other ways to show an effect on respiration, probably reflecting the fact that the obstetric outcome was the primary end point in most of the studies. Nikkola *et al.* (1997) noted a SaO_2 > 95% in all parturients receiving either EDA with 0.5% bupivacaine or IVPCA fentanyl. Jain *et al.* (2003) did not report any parturient with a respiratory rate < 8 when EDA was compared with intramuscularly administered opioids. Halpern *et al.* (2004) noted no respiratory depression in the group assigned to EDA, while there was one case with a respiratory rate < 8 in the group receiving fentanyl IVPCA.

Nitrous oxide has been observed to be associated with maternal hypoxaemia. In a case report, Lucas *et al.* (2000) described a parturient using 50% nitrous oxide with oxygen who was found to be centrally cyanotic and poorly responsive. She had a respiratory rate of < 10 and desaturation periods with nadir of 70% during the contraction pauses. Contractions were no longer followed by desaturation after the patient stopped using nitrous oxide. In a study by Deckardt *et al.* (1987), the parturients inhaled 50% nitrous oxide with oxygen irregularly, which was followed by pronounced decreases in SaO_2. Desaturation periods with the use of nitrous oxide have also been noted in other studies - especially when the use of nitrous oxide is superimposed with that of an opioid analgesia (Reed *et al.* 1989, Griffin *et al.* 1995). In nonrandomised studies, however, parturients may have chosen to breathe nitrous oxide when pain was more pronounced. The possibility can therefore not be excluded that the effect of nitrous oxide on respiration was – at least partially – caused by the pain. In order to further study the respiratory effects of nitrous oxide, Wilkins *et al.* (1989) asked non-pregnant volunteers to hyperventilate 50% nitrous oxide in oxygen and two different concentration of nitrogen in oxygen in a cross-over study which demonstrated that there is a longer period of SaO_2 being decreased below the baseline recording after breathing nitrous oxide in 50% oxygen than when the nitrous oxide was replaced by nitrogen 50% or 79%. The writers suggested various mechanisms to

explain the phenomenon, including diffusion hypoxia, mismatch of pulmonary circulation and ventilation and a depressant effect on the ventilatory drive.

In contrast to the reports of hypoxaemia during nitrous oxide analgesia, at least two more recent cross-over studies found no hypoxaemia. There were no cases of desaturation < 98%, end-tidal carbon dioxide of < 5 kPa or periods of apnoea when 50% nitrous oxide in oxygen was given during 10 contraction study periods by Yeo *et al.* (2007). Carstoniu *et al.* (1994) noted improved oxygenation during a short study period employing 50% nitrous oxide with oxygen compared with a placebo inhalation of compressed air. The possible explanations for the different outcome in the cross-over studies include a bias caused by the intensive study design keeping the parturient more alert. Also, during a short study period the increase in FiO_2 given with nitrous oxide seems to serve as an oxygen supplement. This could be the reason why Arfeen *et al.* (1994) found a higher overall median SaO_2 with nitrous oxide analgesia than EDA although the desaturation periods were longer and more severe with nitrous oxide. An increased FiO_2 is no guarantee against hypoxemic swings, however, as demonstrated by Zelcer *et al.* (1989) who recorded minimum SaO_2's of 75–77% in two parturients with an FiO_2 of 0.55–0.62 when they inhaled nitrous oxide in oxygen.

2.5.2 Sedation

Most studies concerning labour analgesia have used an observer rating of sedation (table 3). Volikas *et al.* (2005) recorded hourly sedation during remifentanil analgesia on a 4-point scale (1 = alert, 2 =slightly drowsy but alert to voice, 3 = drowsy but responds to gentle stimulation, 4 = very drowsy) noting 22 out of 50 women being rated with score of 2 for ≥2h, but this was the highest recorded level of sedation. Blair *et al.* (2001) used both subjective scoring with VAS (0–10) for sedation and observer scoring (1 = awake, 2 = drowsy, 3 = rousable to voice, 4 = rousable to touch, 5 = unrousable) noting only a mild increase in observer score with a median of 2 at a larger PCA bolus of 0.5 µg/kg while the subjective median score increased from 2 at baseline to 4 at a smaller bolus of 0.25 µg/kg and further to 6 at the larger one. Balcioglu *et al.* (2007) noted a declining pattern in the sedation scores during a 90 minute recording using also a 4-point scale with slightly different verbal expressions given for the observer.

Table 3. Cross-over or rescue EDA and side effects during remifentanil labour analgesia. N = total number of patients in the study, n = number of events, FHR = foetal heart rate, VAS = visual analogue scale, RCT = randomised controlled trial, R = remifentanil, P = pethidine, RR = respiratory rate, O_2 suppl= supplemental oxygen, VI = Variable infusion, VB = Variable bolus. Data are mean or median for continuous variables and % for proportions.

Study / N	Type of study	Crossed over to EDA	Nausea	Sedation	Hypoxaemia	FHR abnormal	Apgar score 1/5 minute	Other
Olufolabi *et al*. 2000	Open	100%	75%	Ramsay[a] 2–3:	75%	–	≥9/≥9	Severe pruritus 1
N=4				100%				Minimum SaO_2: 87%
Blair *et al*. 2001	Open		Vomiting:	Subjective:6	SaO_2<90%: 24%	FHR <110:	8/9	VAS (0-10) for nausea, anxiety, and sedation.Observer score for sedation (1–5)
N=21	study	38%	48%	Observer: 2 = drowsy		10% during 2nd stage		Dizziness 9/21
								1 baby received naloxone
Volikas & Male 2001	RCT		Needed antiemetic:	–	–	–		Nitrous oxide (n): R 4, P 5
N=17								Neonate to special care (n): P 0/9, P 1/8
R=9		R 0%	R 22%				R 9/10	Study interrupted due to lower Apgar scores in
P=8		P 13%	P NA				P 5.5/7.5	the pethidine group
Thurlow *et al*. 2002	RCT		Nausea + vomiting:	VAS 0-100 mm:	SAO_2≤94%:	–	No difference	Nitrous oxide: R 56%, P 81%
N=36				No difference				Antiemetic treatment: R 17%, P NA
								RR<8:
R=18		R 39%	R 28%	between R	R 39%			R 3/18
P=18		P 17%	P56% (p=0.06)	and P	P 11%			P 0/18
Volikas *et al*. 2005	Open		No change	Sedation	RR >12:	Suspicious: 30%		Minimum SaO_2: 93%
N=50	study		from baseline	score 1[b]:		Pathological: 30%		No change in sedation from baseline
		10%		44%	100%		9/9	FHR NICE guidelines
								UApH <7.2 (n): 7/37, UABE<-10 (n): 2/34
Blair *et al*. 2005	RCT		60 minute	60 minute	Time spent SaO_2	Dublin RCT-		Nitrous oxide: R 18, P 19
N=39			VAS (0-10):	VAS (0-10):	< 94% or <90%:	method abnormal:		Cord blood pH: R 7.34, P 7.34
R=20		R 10%	R 0	R 8		R 7%	R 8 / 9	NACS lower with pethidine
P=19		P 26%	P 0	P 6	No difference	P 42%	P 8 / 9	

Study / N	Type of study	Crossed over to EDA	Nausea	Sedation	Hypoxaemia	FHR abnormal	Apgar score 1/5 minute	Other
Evron *et al.* 2005	RCT		Nausea and vomiting:	60 minute Ramsay [a]:	SaO_2 1 hour of analgesia:	Loss of variability:	<7:	Cord blood pH: R 7.3, P 7.2
N=88								
R=43		R 10.8%	R 0%	R 1.1	R 97.5%	R 7.8%	R 0%/0%	
P=45		P 38.8% (p<0.007)	P 11%	P 2.6 (p<0.001)	P 94.2% (p<0.001)	P 28.8% (p<0.001)	P 0%/0%	
Balki *et al.* 2007	RCT		Nausea Vomiting	MOAA[c]:	SaO_2 <95%:	Non-reassuring FHR:	<7:	Sedation score 2 in one case
N =20								UAPh:7.24–7.25
						15%	10% / 0%	No naloxone requirement (neonate)
VI=10		VI 10%	VI 20% VI 10%	VI 4.8	VI 40%			Resuscitation of the newborn 5%
VB=10		VB 0%	VB 60% VB 40%	VB 4.4 (p=0.06)	VB 60%			
Balcioglu *et al.* 2007	Systematically RCT			Score 0– 3:	RR<6:	–		No difference in the side effects between the groups
N=60		2%	8%	0–1 minute	0%		8–10/8–10	Sedation decreasing over 90 minutes
								Naloxone, neonate: 0%
Hodgkinson & Hughes 2008	Audit	–	–	–	SaO_2<90%: 17.7%	non-reassuring: 15.2%	8-9: 80.5% / 96.5%	Nitrous oxide used by 84.5%
N=612					O_2 suppl: 17.2%			Withdrawn due to hypoxia 5
								No naloxone (neonate)
Harbers *et al.* 2008,	Open study	–	–	–	O_2 suppl: 7%	–	<7:	Hypotension treated: 3%
N=305							–/ 0.7%	
D'Onofrio *et al.* 2009	Open study	–	Nausea: 1%	OAA/S grade 2-3:	SaO_2<96%: 0%	Variability: No difference from baseline	9/9	Naloxone, neonate: 0%
N=205			Vomiting: 0%	4%	O_2 suppl: 0%			
Evron *et al.* 2008	RCT		–	–	–	–	No difference between groups	Temperature increase: EDA>R
N= 213								
R 44, EDA 99, R+EDA 49		R 0%						
Foley & Hill 2009	Audit	10.5%	–	–	–	–	–	
N=10816, R 1374								
Tveit & Rosland 2009	Open study		–	–	O_2 suppl:	–	<8:	No maternal haemodynamic instability
N = 41		7%			27%		10% / 0%	Naloxone, neonate: 0%

[a] Ramsay score 2–3 (1=anxious and agitated or restless, or both, 2=co-operative, oriented, and tranquil, 3=responds to commands only, 4–6 deeper sedation)

[b] Sedation score (1–4): 1=Slightly drowsy but alert to voice

[c] MOAA=Modified Observer's Assessment of Alertness: 5=responds readily to name spoken in normal tone, 4=lethargic response to name spoken in normal tone, 3=responds only after name is called loudly, 2=responds only after mild prodding and shaking, 0–1=deeper sedation

Balki *et al.* (2007) used the Modified Observer's Assessment of Alertness / Sedation Scale. It was noted that there was milder sedation when the infusion was titrated according to the parturient's need for analgesia in comparison with titration of the PCA bolus (mean lowest sedation score 4.4 with variable infusion vs. 3.4 with the variable bolus, $p = 0.01$). There was one parturient in the study by Balki *et al.* who scored a sedation score of 2 (responds only after mild prodding and shaking) after a 0.5 μg/kg PCA bolus and a background infusion of 0.025 μg/kg/min. Among the published case reports of remifentanil used in obstetric analgesia, there is also one reported case of unconsciousness with apnoea and foetal bradycardia. This event took place when a continuous infusion of remifentanil was increased from 0.05 to 0.1 μg/kg/min. The parturient was ventilated via bag and mask and she regained consciousness upon entering the operating room before naloxone was given (Waring *et al.* 2007).

In the studies comparing remifentanil analgesia with that provided by pethidine, Evron *et al.* (2005) used the Ramsay score (1 = anxious, 6 = unarousable) and noted a consistently milder sedation with remifentanil than with pethidine (mean score 1.1–1.2 vs. 2.6–2.8, respectively, $p < 0.001$) at the three observation points (1 hour after start of analgesia, and at the end of the 1st and 2nd stages), although remifentanil was associated with lower pain scores. Other researchers noted no differences in the sedation scores between remifentanil and pethidine using the subjective VAS and an observer scale (Blair *et al.* 2005, Thurlow *et al.* 2002).

EDA seems to be relatively free from the side effect of sedation. Philipsen & Jensen (1990) asked parturients to assess sleepiness with a VAS (0–100 mm) noting a significantly lower score in the group assigned to EDA (mean 10 mm) compared to 40 mm with pethidine analgesia ($p = 0.001$). Sharma *et al.* (1997) reported median (25th–75th percentiles) sedation scores of 0 (0–0) and 1 (0–2) in EDA and pethidine IVPCA groups in a large study including 715 parturients on a categorical observer scale (0 = awake and alert, 1 = awake but drowsy, 2 = asleep but arousable, 3 = asleep but difficult to arouse, 4 = unresponsive) ($p < 0.001$). This finding was consistent with other studies comparing EDA with long-acting systemic opioids (Sharma *et al.* 1997, Nikkola *et al.* 1997, Jain *et al.* 2003, Halpern *et al.* 2004).

In the pilot study with 5 parturients, Klikowitsch (1881) noted that consciousness was maintained although crying ceased and the women either moaned slightly or were completely quiet. In later publications, the danger of too deep a sedation has been noted in the Report of the Committee on Nitrous Oxide

and Oxygen analgesia in Midwifery (1970) where 0.4% of the 259 parturients and 3% of the 242 parturients were reported as having become unconscious with 50% and 70% nitrous oxide, respectively. The proportions of mothers who were reported to have fallen asleep during contractions were 16.6% and 21.7% with the two mixtures of nitrous oxide and oxygen. Moreover, McAneny & Doughty (1963) reported an increase in the proportion rendered unconscious during inhalation of nitrous oxide from 1% with 50% N_2O to 5% with 80% N_2O. The subjective median VAS (0–100 mm) score for sedation during intermittent 50% nitrous oxide analgesia was 51 mm (range 13–100) in a cross-over study by Yeo *et al.* (2007). None of the 32 parturients included in the study experienced excessive drowsiness in spite of the fact that the sedation scores were even higher, 74 mm (range 33–100), during the study periods when the parturients were using sevoflurane. There were no cases of unconsciousness in two smaller nitrous oxide studies (Westling *et al.* 1992, Carstoniu *et al.* 1994).

2.5.3 Nausea and vomiting

Nausea is often experienced by parturients and it is difficult to say in clinical studies to what extent the observed nausea is actually caused by the treatment and what proportion of nausea is part of the normal, physiologic course of labour. Parsons *et al.* (2007) noted that 28–32% and O'Sullivan *et al.* (2009), in a large RCT of 2426 nulliparous women, 34–45% of parturients vomited during labour with no difference in whether the women were fasting or whether they ate during labour. During labour, gastric emptying is prolonged and its pattern altered as revealed by Davison *et al.* (1970). Systemic opioid treatment slows gastric emptying while the modern low-dose epidural analgesia using a mixture of local anaesthetic and opioid does not, especially if the cumulative fentanyl dose does not exceed 100 μg (Nimmo *et al.* 1971, Porter *et al.* 1997).

Problems with studying nausea include its subjective nature and the fact that nausea fluctuates with time. In an old study, only objective signs referred to as toxic effects (including eg. dizziness, sweating and retching) were noted, resulting in only 11 out of 500 parturients receiving pethidine being reported as suffering from this side effect (Barnes 1947). Opposed to this, midwife observers noted nausea in approximately 18% during 1 hour before giving any analgesic treatment. Pethidine caused an increase to approximately 33% at one hour after the pethidine injection of 100–150 mg (route not reported, Vella *et al.* 1985), but the criteria for nausea were not specified. It seems that in most studies, the proportion of women

vomiting is smaller than those with nausea. In a study including only primiparous parturients, Keskin *et al.* (2003) noted a 21% and 47% incidence of nausea and 10% and 7% incidence of vomiting at 30 minutes after IM tramadol and pethidine, respectively. The report did not specify the method by which nausea had been detected. It mentioned only that parturients were examined at certain intervals in order to evaluate changes *inter alia* in symptoms of vomiting and fatigue. Bofill *et al.* (1997) noted a similar proportion of women (11%) vomiting and reporting nausea without emesis, however, in their sample of 100 parturients with no difference between women randomised to receive intravenous butorphanol with anti-emetic or EDA. Again, the paper did not state their method for assessing nausea.

There is a wide variation in the incidence of nausea and vomiting reported in the studies concerning remifentanil for labour analgesia (table 3) which may be explained by differences in the methods used for assessing these variables. The least nausea (incidences of 0–1.5%), however, was reported in papers with the largest decrease in pain scores from the baseline, which is in accordance with earlier observations of postoperative pain being a reason for nausea and that pain relieving medications have an antiemetic effect (Andersen *et al.* 1976). One could also speculate that the use of a background infusion or a continuous infusion may reduce peak concentrations at the effect-site, thereby reducing subjective side effects - especially when the peaks coincide with the contraction pauses. Indeed, one of the papers reporting a low incidence of nausea employed a continuous infusion (D'Onofrio *et al.* 2009). Balki *et al.* (2007) also observed remifentanil analgesia during the entire course of labour in 20 parturients and noted a 40% incidence of nausea and 25% of vomiting, with a trend towards more side-effects in the group in whom the PCA boluses were increased according to need compared with the group whose background infusion was titrated. A background infusion was also used by Balcioglu *et al.* (2007). During a 90 minute observation time, they noted nausea in 5 out of 60 parturients in the study with the highest consumption of remifentanil. The relatively low incidence of nausea could suggest that this side effect is not dose dependent. In a meta-analysis concerning intrathecal morphine, a larger dose of opioid seemed to be associated with a lower incidence of vomiting (Gehling & Tryba 2009). Volikas *et al.* (2005) gave metoclopramid as an antiemetic with remifentanil analgesia and reported no change in nausea from the baseline. None of the four studies comparing remifentanil and pethidine analgesia observed a significant difference in nausea and vomiting between the two medications. In the study by Thurlow *et al.* (2002),

however, pethidine was accompanied with a prophylactic antiemetic. In spite of this, there was a trend towards more nausea in the pethidine group.

Epidural analgesia may have a protective effect against nausea and vomiting. In a large study concerning complications during labour analgesia, Norris *et al.* (1994) noted an incidence of only 1% for both nausea and vomiting. A more historical study by Hollmén *et al.* (1977) reported a 3% incidence of nausea and vomiting. In contrast, Philipsen & Jensen (1990) noted as much vomiting with systemic opioid analgesia (20%) as with EDA (22%). The nausea score was only 3 mm on a VAS of 0–100 mm in both groups. In that study, the EDA was also allowed to wear off at the beginning of the 2nd stage, resulting in no difference in the 2nd stage pain between the groups. It is possible that there was an increase in nausea and vomiting during the increase in pain towards the end of the labour. Unfortunately, the side effects were not reported separately for the two stages of labour. An antiemetic given with opioid analgesia may result in nearly as low an incidence of nausea and vomiting with opioid analgesia as noted with EDA. Bofill *et al.* (1997) reported nausea without emesis in 10% and 12% (NS) of women randomised to EDA and systemic opioid analgesia with butorphanol with promethazine as an antiemetic. There was a large proportion (25%) of crossing-over from the opioid therapy to EDA as well, however, which could have had a diluting effect on the nausea observed in the opioid arm of the study. Sharma *et al.* (1997) reported 7% and 4% incidence of nausea and vomiting in EDA and IVPCA with pethidine and promethazine as an antiemetic, respectively, in a large study including 715 parturients. The use of prophylactic antiemetics in two of the three studies incuded in a meta-analysis may also have influenced the conclusion by Leighton and Halpern that there is no difference between EDA and systemic opioid analgesia concerning nausea (Leighton & Halpern 2002). Later, Halpern *et al.* (2004) reported a 17% and 6.4% use of antiemetic therapy in the opioid and EDA groups, respectively ($p = 0.01$) in a study with no antiemetic prophylaxis.

Nausea and vomiting has been reported in 5–36% of women in nitrous oxide studies reviewed by Rosen (Rosen 2002). In another systematic review by Kronberg & Thompson (2005), it was concluded that nitrous oxide "likely does not further contribute to nausea and vomiting associated with labor". This was based on the reported relatively small incidence of nausea (5–20 %) in one Chinese and two British studies. In one of the two British studies, however, McAneny & Dougthy (1963) noted a 22% incidence in the groups receiving 70–75% nitrous oxide while the incidence was 16% with a concentration of 50%, suggesting a dose-response relationship when higher concentrations are employed.

In comparison with sevoflurane, nitrous oxide resulted in more nausea (26% vs. 3%) and vomiting (13% vs. 0%) in a cross-over trial (Yeo *et al.* 2007). It is possible that sevoflurane served as an antiemetic rather than nitrous oxide causing nausea. It seems that one could say that while the conclusion of Kronberg and Thompson (2005) may be true, nitrous oxide is probably not a potent antiemetic either, in spite of the fact that Klikowitsch made experiments in diminishing nausea with it (Richards *et al.* 1976).

The mechanism of opioid-induced nausea, as well as that of nausea experienced during non-medicated labour remains unclear. The fact that effective labour analgesia such as an epidural block is associated with a low incidence of nausea and vomiting suggests that at least a proportion of nausea comes with pain. Another possible reason for nausea during labour is hormonal. Menstrual variation in PONV suggests nausea is dependent of hormonal changes (Honkavaara *et al.* 1991). Nausea during pregnancy has also been thought to be caused by human chorionic gonadotropin and estradiol. As smoking is associated with less of a risk for nausea and vomiting in pregnancy, an interesting theory has been suggested according to which this observation is caused by diminished human chorionic gonadotropin among smoking pregnant women (Goodwin 2002). Another suggested mechanism for nausea during pregnancy is mediated through the vestibular system with a link between a history of motion sickness and vomiting during pregnancy (Black 2002). It appears that the suggested mechanisms of nausea during labour may be related to the classic risk factors for PONV (motion sickness and not smoking) suggested by Apfel *et al.* (2002).

2.5.4 Other maternal side effects

Remifentanil appears to be haemodynamically inert in the doses used in labour analgesia with no difference from the values obtained with pethidine (Thurlow *et al.* 2002, Volikas *et al.* 2005, Blair *et al.* 2005, Evron *et al.* 2005, Balcioglu *et al.* 2007). Harbers *et al.* (2008) reported 9 cases of hypotension during remifentanil labour analgesia, but the cut-off value for hypotension was not reported. These were treated with an infusion of crystalloid solutions. Itching has been observed in some remifentanil studies (Olufolabi *et al.* 2001, Balki *et al.* 2007, Blair *et al.* 2001). Olufolabi *et al.* (2000) described a strong facial pruritus in one case but Volikas & Male (2001) did not find a difference the incidence of itching from that of pethidine. Volikas *et al.* (2005) observed a significant increase in itching scores during remifentanil analgesia, but the pruritus was graded as modest and required

no treatment. Dizziness seems to be a more consistent finding, as noted in 20–43% of parturients (Balki *et al.* 2007, Blair *et al.* 2001).

Epidural analgesia is associated with a 7–22 % risk of hypotension (Hollmén *et al.* 1977, Norris *et al.* 1994, Jain *et al.* 2003, Ramin *et al.* 1995). Leighton & Halpern (2002) noted hypotension with an odds ratio of 74.2 in a meta-analysis of RCTs comparing EDA with systemic opioid analgesia ($p < 0.001$). EDA is associated with urinary retention in 2.7–40% of cases (Skupski *et al.* 2009, Philipsen and Jensen 1989, Jain *et al.* 2003, Olofsson *et al.* 1997). Hyperthermia associated with EDA has been documented, but this is a finding based on a comparison of EDA with systemic opioid analgesia. Leighton & Halpern (2002) suggested that the difference in maternal temperatures between the two analgesic methods could be a result of the hypothermic properties of pethidine rather than hyperthermic effect of EDA. This hypothesis was supported by the findings of the study by Evron *et al.* (2008). A trend towards lower temperature was seen in the groups receiving either remifentanil only or remifentanil with EDA in comparison with EDA only. Unintentional dural puncture has been noted with EDA and CSE with an incidence of 0.5–3.6% (Norris *et al.* 1994, Gleeson & Reynolds 1998, Aya *et a.l* 2001, Pan *et al.* 2004, Van de Velde *et al.* 2008). EDA seems to increase the duration of the second stage of labour (Leighton & Halpern 2002). An increased risk for instrumental vaginal deliveries was greater in women randomised to EDA in a meta-analysis of 17 trials (Anim-Somuah *et al.* 2005) Transient and persistent neurological injury has been estimated to occur in 1 out of 6700 and 1 out of 240,000 mothers with EDA (Ruppen *et al.* 2006). In a Swedish study including 255,000 neuraxial blocks, 10 mothers were found to have suffered severe complications (Moen *et al.* 2004).

Nitrous oxide causes a dose dependent decrease in maternal heart rate (HR), cardiac output and blood pressure (BP) in the mother, which has been thought to be a result of the dose dependent reduction of pain (Westling *et al.* 1992). Klikowitsch measured the intrauterine pressure during nitrous oxide labour analgesia in three cases and noted that there was no effect on the strength, frequency and duration of the uterine contractions. These observations have been later confirmed and it seems that nitrous oxide has no effect on the progress of labour (Klikowitsch 1881, Rosen 2002).

2.6 Foetus and the neonate

2.6.1 Foetal heart rate (FHR) tracing

The widespread use of electronic foetal heart monitoring has not fulfilled the promise of reducing neonate disability, even though an increase of emergency caesarean sections has been witnessed (Graham *et al.* 2006). FHR does provide, however, valuable information concerning foetal wellbeing. Volikas *et al.* (2005) followed FHR closely for 20 minutes after the initiation of IVPCA with remifentanil, noting changes in 10 cases out of 50. In four cases the changes included a reduction in the baseline by 10–20 beats /min. Reduced beat-to-beat variability was noted in 3 tracings and decelerations down to 100–120 beats/minute were noted in 3 cases. None of the changes required obstetric intervention. Blair *et al.* (2005) analysed FHR tracings during 1 hour after the commencement of analgesia and noted a trend towards more traces remaining normal with remifentanil compared with pethidine (93% vs. 58%, respectively, NS). Evron *et al.* (2005) noted more missing reactivity, loss of variability, variable decelerations and a combination of the latter two abnormalities in the pethidine group as compared to remifentanil analgesia. The reported incidences of FHR changes during remifentanil analgesia are included in table 3 which also depicts the variety of different criteria for interpreting the tracings.

Loss of variability is a typical finding with opioid labour analgesia. Harmer & Rosen (1996) pointed out that the significance of reduced beat-to-beat variability during opioid analgesia is uncertain, but that the phenomenon is probably innocent. It is probably a product of a direct effect on the central nervous system of the foetus with no link to problems in foetal oxygenation as observed by Alahuhta *et al.* (1993) with Doppler velocimetry in cases with reduced FHR variability as a result of administration of 50 µg of sufentanil epidurally during labour. Nevertheless, a sustained lack of baseline variability serves as an indicator of foetal distress and there is a possibility of opioid-induced FHR changes masking a warning sign in the electronic foetal monitoring.

Changes in the FHR associated with remifentanil analgesia raise the question of whether the delivery mode might be affected, especially with regards emergency obstetric interventions. Table 4 sums the experience gained so far with delivery mode in labours with remifentanil analgesia. A bias is possible due to the fact that those labours during which the parturient needed neuraxial analgesia were not included in the analyses in all the papers. Nevertheless, it seems that

remifentanil analgesia is not associated with a higher incidence of caesarean section (CS) or instrumental vaginal deliveries than has been summarised by Leighton & Halpern (2002) for neuraxial analgesia and long-acting opioids. Three papers comparing remifentanil with pethidine in labour analgesia suggest that there is no significant difference in rates of emergency caesarean section and instrumental vaginal delivery in comparison with pethidine (table 3, Volikas & Male 2001, Thurlow *et al.* 2002, Evron *et al.* 2005).

Neuraxial analgesia may also not be innocent with regards a causal link to emergency caesarean sections and instrumental vaginal deliveries due to findings in FHR tracings. In a large RCT by Gambling *et al.* (1998), none of the 607 parturients assigned to receive pethidine delivered by CS due to profound foetal bradycardia while there were 9 such cases in the combined spinal epidural (CSE) group of 616 parturients. According to the review by van de Velde (2005b) this is, however, the only study indicating an increase in operative deliveries due to FHR changes in neuraxial analgesia. Problematic FHR changes occur in 3.9–15.4% during CSE analgesia and 2.5–18.8% during EDA according to retrospective trials (Van de Velde 2005). In a prospective double blind, randomised study, IT sufentanil 7.5 μg was associated with a 24% incidence of foetal bradycardia or late decelerations in contrast with 11–12% with a mixture of IT bupivacaine, epinephrine and only 1.5 μg of sufentanil or EDA. In the presence of a protocol for foetal resuscitation, however, the FHR abnormalities were not reflected as an increased rate of emergency CS (Van de Velde *et al.* 2004). A more recent RCT found prolonged deceleration in 6.2% and 3.2% in CSE and EDA groups, respectively (Skupski *et al.* 2009). The overall incidence of FHR changes was 7.9% with EDA. The rates of CS and instrumental vaginal delivery (vacuum extraction or forceps) with neuraxial analgesia during labour have been reported as 8% and 19%, respectively in a systematic review with no difference in caesarean rates but an increase in instrumental vaginal deliveries compared to systemic opioid analgesia (Leighton & Halpern 2002). In the abstract presented by Foley and Hill (2009) which contributed most of the cases to table 4, the incidence of emergency caesarean delivery and instrumental vaginal delivery for EDA were 21.7% and 39.7%, respectively. However, this observation in a nonrandomised cohort is probably influenced by the fact that women with high pain intensity and distress are be more likely to request labour analgesia early and have longer latent and active phases of labour. Moreover, they are at increased risk for occurrence of abnormal FHR during labour and for obstetric interventions (Wuitchik *et al.* 1989). Nevertheless, the available data suggest that in

comparison with EDA, remifentanil analgesia does not seem to increase the rate of operative deliveries.

Table 4. Remifentanil analgesia and delivery mode.

Study	Parturients receiving remifentanil	Caesarean section	Ventouse or forceps
Blair *et al.* 2001	21	3	2
Volikas & Male 2001	9	2	2
Thurlow *et al.* 2002	18	3	4
Volikas *et al.* 2005	50	7	10
Evron *et al.* 2005	43	3	2
Balki *et al.* 2007	20	2	1
Balcioglu *et al.* 2007	60	2	1
Harbers *et al.* 2008	305	43	50
Foley & Hill 2009	1374	33	234
D'Onofrio *et al.* 2009	205	17	9
TOTAL	2105	115 (5%)	315 (15%)

2.6.2 Cord blood gas analysis

Umbilical cord acid-base analysis provides information on the function of the placenta and the foetal circulation immediately before delivery. The lower limit for normal UApH has been defined as 7.1 and base excess (BE) as -11 based on observed values of - 2 SD or 2.5 percentile in a population with 5 minute Apgar ≥ 7 (Helwig *et al.* 1996). The mean cord pH after remifentanil analgesia has been reported as 7.2–7.34 (Blair *et al.* 2005, Evron *et al.* 2005, Balki *et al.* 2007). Blair *et al.* (2005) and Evron *et al.* (2005) reported that cord blood pH was similar with remifentanil and pethidine analgesia. Volikas *et al.* (2005) noted 7 cases with a pH < 7.2 in a series of 37 cases and BE <-10 in 2 cases out of 34. Epidural analgesia is associated with better pH in randomised trials and better BE when both randomised and observational studies were included in the meta-analyses compared with the values with long acting systemic opioids (Reynolds *et al.* 2002). In absolute figures, the mean UApH was 7.22–7.36 in the studies after EDA suggesting little or no difference from the results of remifentanil studies in table 3. The comparison of results gathered from entirely different studies should, however, be done with caution. Nitrous oxide analgesia during the 2nd stage of labour had no effect on UApH or BE as noted by Abboud *et al.* (1981).

Maternal ventilation is reflected in the cord blood gas analysis. Severe hyperventilation ($paCO_2$ < 2.3 kPa) results in acidosis and a delayed onset of

respiration in the newborns as noted by Moya *et al.* (1965), based on a study with women delivering with an experimentally manipulated respiration. There were actually only 2 parturients with such severe hyperventilation in that study with 85 women. In spite of the small number of cases with severe hypocapnia, this observation turned out to be important as a starting point for further investigations. Motoyama *et al.* (1967) noted a decrease in the oxygen content of the foetal carotid and umbilical venous blood when pregnant ewes were experimentally made alkalaemic. A decrease in oxygen supply to the foetus of more than 10% with a change of 0.1 pH unit caused by maternal respiratory alkalaemia was established. The mechanism by which the changes in CO_2 tension influence oxygen delivery to the foetus was first thought to be related to a regulation of vascular resistance according to maternal partial gas tension of CO_2 in a similar way as has been confirmed for the circulation in the brain. Levinson *et al.* (1974) showed, however, that uterine blood flow was not affected by changes in maternal CO_2 or pH. Instead, an explanation based on the shifts in the oxyhaemoglobin dissociation curve was discovered. Moreover, it was shown that maternal hypoventilation is associated with improved oxygen release, even though the umbilical venous pH follows the maternal pH in to respiratory acidosis (Motoyama *et al.* 1967). Deckhardt *et al.* (1987) noted that pain-induced changes in respiration during labour and delivery led to a more acidic status of the neonate when they compared the UApH in deliveries by parturients with EDA scoring pain as 3.5 on VAS (0–10) with that of those without EDA scoring pain as 7.1 (mean UapH 7.29 and 7.21, respectively, $p = 0.01$). It was suggested that pain stimulates breathing causing hypocarbia which in turn shifts the oxyhaemoglobin dissociation curve to the left. As a result, the release of oxygen from maternal haemoglobin is reduced in placenta.

In the study by Porter *et al.* (1992) no correlation existed between maternal hypoxaemia, umbilical cord gas measurements, and the neonatal oxygen saturation values. This probably reflects the fact that an uncompromised foetus has reserves with which temporary decreases in the oxygen content in the placental circulation have no effect on the foetal well-being. The situation may be different, however, in the case of a compromised foetus.

2.6.3 Effects of maternal analgesia on the neonate

Neonatal depression may be obvious leading to use of an antidote (naloxone if opioid effect is suspected), resuscitation of the newborn or a need for neonatal

intensive care. Frank respiratory depression is reflected in the Apgar scores and time to sustained respiration (Apgar 1953). A more subtle tendency of respiratory depression from exposure to opioids has been noted by giving the neonate an injection of naloxone and observing whether there is an increase in the respiratory rate (Belfrage *et al.* 1981) and with monitoring the haemoglobin oxygen saturation over the first hours after delivery (Nikkola *et al.* 2000). Measuring respiratory indices such as respiratory rate, tidal volume, minute volume and lung compliance showed differences in neonates at 2h of age (Faxelius *et al.* 1983). The noted differences were thought to be caused by an increased level of catecholamines at birth associated with vaginal delivery. Other subtle forms of neonatal depression can be assessed with neurobehavioral testing such as neonatal adaptive capacity scoring (NACS), but this method has been criticised for lack of correlation with clinical end-points and reliability (Brochurst *et al.* 2000, Halpern *et al.* 2001). The newborns' ability to start breast-feeding has also been assessed by video recording the spontaneous movements of the neonate during the first hours after delivery (Ransjö-Arvidsson *et al.* 2001). All these methods of assessing the neonate are surrogate variables for potential morbidity, mortality or other clinical end points such as successful initiation of breast-feeding. The importance of small deviations often referred to is unknown while frank deviations - such as a 5 minute Apgar score less than four - are more clearly associated with a poor prognosis (Hogan *et al.* 2007). The link between poor results in neonatal assessment and possible damage is a hypoxic insult. Less information is available concerning the clinical significance of neonatal scoring when maternal analgesia is the reason for depression.

The fact that remifentanil is eliminated as fast in the neonate as in the mothers is well documented (Ross *et al.* 2001). It appears that the advantage of a short elimination in comparison with longer acting opioids also holds true with preterm babies. After termination of infusions of morphine or remifentanil in intensive care for respiratory distress syndrome, the length of time required to awaken and extubate the neonates was 18.9- and 12.1-fold longer, respectively, in the morphine group than in the remifentanil group (Silva *et al.* 2008). The first of the four RCTs comparing remifentanil and pethidine in labour analgesia was interrupted due to the lower Apgar scores in the pethidine group in an interim analysis of the data (Volikas and Male 2001). The finding was not, however replicated in the later studies (Thurlow *et al.* 2002, Blair *et al.* 2005, Evron *et al.* 2005). Evron *et al.* (2008) noted that there was no difference in heart rate (HR), non-invasive blood pressure or SaO_2 between babies born to mothers receiving

remifentanil, EDA or both of the medications. The neonates scored better in neurobehavioral testing at 30 minute after delivery in a RCT comparing remifentanil with pethidine (Blair *et al.* 2005).

In a nonrandomised study, those newborns whose mothers received pethidine or bupivacaine or more than one type of analgesia during labour showed less movements which are thought to be associated with successful breast-feeding (such as massage-like hand movements, hand-to-mouth movements, touching the nipple with their hands before suckling, licking movements and sucking the breast), than did babies born with non-medicated labours (Rannsjö-Arvidsson *et al.* 2001). In a cohort in the North of Finland, breast-feeding problems as well as mixed or full bottle feeding were more common among those receiving EDA (Volmanen *et al.* 2004). Observational studies concerning EDA are, however, subject to selection bias. Moreover, there are studies with no difference in breast-feeding performance (Halpern *et al.* 1999). In a systematic review, Leighton and Halpern (2002) concluded that EDA does not affect breast-feeding initiation or management. The question of whether EDA would still be linked with breast-feeding failure was raised again when Beilin *et al.* (2005) noted in a RCT that those women who received more than 150 μg of fentanyl in the EDA were less likely to continue breast-feeding at 6 weeks after delivery. In this respect, one could speculate that an ultra-short analgesic may have an advantage over longer acting medications. Evron *et al.* (2005) noted a trend toward less feeding difficulties in 6.3% and 12.8% of newborns after maternal analgesia with remifentanil or pethidine, respectively. The finding was not statistically significant, however, nor was the way in which the difficulty was assessed specified. Nitrous oxide is thought be safe with respect to neonatal side effects (Rosen 2002).

3 Aims and hypotheses of the present research

In the present investigation, the purpose is to present the main findings of the four original clinical studies concerning the use of remifentanil in labour analgesia related to the dosing of remifentanil and in comparison with nitrous oxide and EDA and to gather together the experience gained during IVPCA with remifentanil in 114 parturients in four clinical studies. Specifically, an effort was made:

1. to determine at what dose remifentanil should be given to labouring women (I, III),
2. to determine the relative potency and side-effects of remifentanil compared with N_2O (II),
3. to determine the relative potency and side-effects of remifentanil compared with epidural analgesia (III),
4. to distinguish whether or not it is possible to improve IVPCA with remifentanil by timing the bolus optimally in the uterine contraction cycle (IV), and
5. to contribute to the global experience concerning the safety of remifentanil analgesia during labour (I-IV).

The hypotheses tested in the original studies were:

1. that remifentanil would provide better analgesia during labour than N_2O (II),
2. that remifentanil could provide as satisfactory an analgesia as epidural analgesia (III), and
3. that optimising the timing of the remifentanil bolus would improve the analgesia compared with a dose given during the uterine contraction (IV).

4 Patients and Methods

4.1 Patients

After the study protocols were approved by the ethical committee of the Northern Ostrobothnia Hospital District and the National Agency for Medicines, 142 parturients with written informed consent participated in the four studies. Inclusion and exclusion criteria are in table 5. Additional inclusion criteria were used in individual studies according to the specific aims of the studies. These are included in the detailed description of the study designs (below).

The parturients were recruited during the first stage of labour in the Oulu University Hospital during the years 2000–2008. In the study comparing EDA with remifentanil analgesia, parturients were also recruited in the Helsinki University Hospital, the Helsinki Women's Hospital.

Table 5. Inclusion and exclusion criteria.

Inclusion criteria:	Healthy parturient
	Pregnancy at term (>37 wks of gestation)
	First stage of labour (cervical dilatation < 7 cm)
Exclusion criteria:	Complicated pregnancy
	Multiple pregnancy
	Abnormal presentation
	Signs of asphyxia on FHR
	Regional analgesia
	Analgesia with other opioids
	Allergy towards any of the drugs used in the study

4.2 Analgesic techniques and designs of the original studies

All four original studies were prospective clinical trials.

In the dose-finding study (study I), the parturients received remifentanil in a 0.025 mg/ml solution via a PCA infusion pump (Graseby 3300, Graseby Medical Ltd, Watford, UK) programmed to give a bolus over 1 minute with a 1 minute lock-out period. The dose was increased every 10 minutes according to a dose escalation scheme starting from 0.2 μg/kg up to 0.8 μg/kg until the parturient did not wish to have more effective pain relief. The maximum time for the exposure was 60 minutes. There were no control groups and no blinding.

The study comparing remifentanil with nitrous oxide (study II) employed a cross-over design. The parturients as well as the research personnel were blinded as to whether the parturients were subjected to nitrous oxide or remifentanil during a given study period. Remifentanil was given in the same way as in the dose-finding study, but the dose was fixed at 0.4 μg/kg (the median effective dose as determined in the dose-finding study). Nitrous oxide was given in the way it is given during routine clinical analgesia i.e. intermittent PCA with 50% nitrous oxide in oxygen. The parturients were randomised into two groups. The difference between the groups was the order in which the medications were given. Saline was given instead of remifentanil during the study period when nitrous oxide was used and compressed air was given instead of nitrous oxide during the remifentanil period. The study periods lasted 20 minutes with a 20 minute wash-out sequence after each study period.

A parallel design was chosen for the comparison of intravenous remifentanil with epidural analgesia (study III). The parturients as well as the research personnel were blinded as to which type of analgesia the parturient was given. According to an additional inclusion criterion the parturients entered the study only when they asked for epidural analgesia. An epidural catheter was then placed after which the parturient received either remifentanil intravenously or a 20 ml bolus of a mixture of local anaesthetic and opioids epidurally (0.0625 mg/ml bupivacaine and 2 μg/kg fentanyl) according to a randomisation list. Remifentanil was given with the protocol as in the dose-finding study, but the dose escalation scheme was different (0.1–0.9 μg/kg). The maximum time of exposure was also 60 minutes in this study.

In study IV, a device was manufactured which delays the PCA signal given by the parturient. This triggered a PCA pump to give a delayed bolus of remifentanil to give the maximum effect at the peak of the following uterine contraction. This pump was used simultaneously with a regular PCA pump, one of the two giving saline and the other giving remifentanil in a solution of 0.02 mg/ml in a double blinded cross-over study. An additional inclusion criterion was used according to which the uterine contraction cycle should not have been less than 4 minutes at recruitment. Between the two study periods there was a washout period during which the syringes were switched between the pumps. Each study period lasted 6–8 contraction cycles.

In studies I, II, and IV a new form of analgesia was instituted after a 20 minute follow-up period, whereas in study III the epidural catheter already in

place was employed as soon as the parturient answered “yes” when asked whether she would like to have more efficient analgesia.

The idea of undertaking a series of studies concerning remifentanil in obstetric analgesia was conceived during discussions between Dr Ethem Akural and the principal researcher. The principal researcher designed the original studies with the support of the cowriters. In study III, Dr Johanna Sarvela and Pekka Halonen gave valuable input for the study design when it was restarted after being extended to the Helsinki University Hospital. The principal researcher conducted the analgesia and collected data in most of the cases. Occasional, but important help was received from the research nurses Päivi Rautio and Jaana Ahola, as well as from Dr Ethem Akural. Dr Johanna Sarvela and Professor Seppo Alahuhta took over conducting the study and collected several cases for studies III and IV in Helsinki and Oulu, respectively, during the absences of the principal researcher. Professor Kari Korttila supervised the study in Helsinki and Seppo Alahuhta for the whole process of the four studies in Oulu. The data analysis was done by the principal researcher with the support of the biostatistician, Mr Pasi Ohtonen.

4.3 Variables and measurements

The basic demographics were recorded during the initial interview with the parturient during the beginning of the study period. Missing data were retrieved from the antenatal clinic card and hospital records. The last weighing i.e. the actual measure was included as the weight.

Classic risk factors for postoperative nausea and vomiting (smoking and history of motion sickness or PONV) were recorded. Factors likely to interfere with labour pain perception and tolerance such as parity, whether the labour was induced medically and the presence of an accompanying support person (doula or husband in studies II-IV only) and attendance to antenatal classes were recorded for each parturient.

The parturient’s perception of an acceptable pain score for the current labour was asked after she had assessed the pain of the uterine contraction before the commencement of the study medications in studies III and IV. In study IV, the baseline pain was recorded as the mean of the pain scores of the last three uterine contractions immediately before the first PCA triggering.

The parturients assessed the pain of each contraction (last contraction in every 10 minutes in studies I and II) on an 11-point numerical rating scale (0 = no pain, 10 = worst pain imaginable). They ranked the pain relief on a 5-point scale

(4 = complete, 3 = good, 2 = moderate, 1 = slight, 0 = no relief) and evaluated sedation, nausea and itching (only in studies I and II) on a 4-point categorical verbal rating scale (3 = strong, 2 = moderate, 1 = weak, 0 = none), at every second uterine contraction. In the study comparing remifentanil with nitrous oxide, however, nausea was scored on an eleven point numerical rating scale similar to that used for pain scoring. At the end of the study period, the parturient was asked whether she would have liked to continue with the given medication if it were in routine use. In studies II-IV, each parturient was asked to indicate which medicine (which timing of the bolus in study number IV) she thought she had been receiving during the study.

Heart rate and SaO_2 were monitored continuously. Non-invasive blood pressure (NIBP) was recorded at 5-minute intervals in the dose-finding study while it was recorded at 10-minute intervals in the other three studies. All physical measurements were made with a Datex anaesthesia monitor (Instrumentarium Corp. Helsinki, Finland). In study I, respiratory rate was monitored with a Datex light monitor based on the changes in the thoracic impedance via the electrocardiogram leads. In study II, a side stream sample was taken for gas analysis from the tubing adjacent to the mask for nitrous oxide (or placebo during the remifentanil period in the cross-over study) in order to monitor $ETCO_2$. Repeated dips in $SaO_2 < 94$ % in study I and a dip < 95% in studies III and IV were treated with supplemental oxygen at a rate of 2 l / minute via a nasal cannula. In studies I and III, during the dose escalation, the dose was recorded at which the need for oxygen supplementation arose. In the dose-finding study (I), SaO_2 and HR values were recorded at 1-minute intervals and NIBP was recorded at 5-minute intervals. In the other studies the SaO_2 and HR values were recorded every 10 seconds with the Datex AS/3 Collect 2.1 software (Instrumentarium Corp. Helsinki, Finland), which was also used for recording the NIBP values measured every 10 minutes.

Uterine activity was monitored with external tocodynamometry and FHR with an internal foetal scalp electrode (cardiotocography, CTG) during the study, and 30 minutes after the study period with a HP 8040A cardiotocogram recorder (Hewlett-Packard, Böblingen, Germany), a Stan S21 Foetal heart monitor (Neoventa Medical AB, Gothenburg, Sweden) or Philips Avalon FM30 (Philips, Böblingen, Germany). The FHR tracings were analysed after completion of patient recruitment in each original study by an obstetrician blinded to the method of analgesia. In study III, the FHR changes were interpreted as pathological if there was an absence of accelerations, decreased variability (< 5 bpm for more

than 5 minutes), bradycardia (> 20 bpm or rate < 100 bpm for more than 1 minute) or late decelerations in studies I-III. The NICE criteria were used in study IV (National Collaborating Centre for Women's and Children's Health 2007). The UapH values of the newborns were recorded. Midwives gave the Apgar scores.

4.4 Data analysis

4.4.1 Analysis in the original studies

The number of parturients included in the individual studies was based on power analyses except for the first study which was planned before any systematic studies were published concerning remifentanil in labour analgesia. For the cross-over study comparing remifentanil with nitrous oxide (II), the calculation of the sample size was based on observations in the previous dose-finding study (SD of 2, considering a 2 point difference in the verbal rating scale (0–10) for pain as clinically significant, and choosing alpha 0,05 and power of 80%) resulting in a sample size of 10 for an analysis of paired data. For the comparison of remifentanil with epidural analgesia (III), the sample size was calculated by considering a two-unit difference in the pain score (0–10) as being clinically significant, with a standard deviation of 2. This would have required 20 individuals per study group (alpha = 0.05, power = 0.8). The sample for the study concerning the timing of the IV-bolus (IV) was determined after an interim analysis of the first 15 cases, determining the variability of the difference between the pain scores during the two exposures with different timing of the bolus during the uterine contraction cycle. Accordingly, the sample size calculation was based on SD 1.8 in the difference of reduction of pain scores (0–10) between the two dosing regimens assuming a 2-point difference as clinically significant between the treatments ($\alpha = 0.05$, $\beta = 0.1$).

It was expected that some parturients could not be included in the analyses due to the progress of labour into the 2nd stage of labour or for technical errors in the conduct of the studies. Hence, the number of parturients included in the studies was chosen to be larger than the calculated sample sizes (table 6).

The parturients' assessments were recorded on a data gathering form. Pain at the baseline before any remifentanil was given was assessed immediately before the commencement of each study. In studies I-III this was the pain score during a single uterine contraction. In study IV, the baseline pain was defined as the mean

of pain scores obtained after three subsequent uterine contractions immediately before the commencement of the first study period. The last scores given during each 10 minutes of the study were included in the analyses in studies I-III. In study IV, three pain scores obtained after three subsequent uterine contractions (4^{th}–6^{th} contractions during each study period) were included.

Table 6. The clinical studies included in the academic dissertation.

Study	Title	Method	N recruited
I	Remifentanil in obstetric analgesia: a dose-finding study	Open study	20
II	Comparison of remifentanil and nitrous oxide in labour analgesia	Double-blinded, randomised, cross-over study	20
III	Intravenous remifentanil vs. epidural levobupivacaine with fentanyl for pain relief in early labour: a randomised, controlled, double-blinded study	Double-blinded, randomised, parallel study	52
IV	IVPCA remifentanil bolus during the contraction pause does not improve the analgesic effect, during early labour	Double-blinded, randomised, cross-over study	50

The averages of the pain scores included in the analyses for each parturient and for each study period were used to calculate the PID as the difference of the pain scores during the treatment and the reference value. Due to the fact that pain intensity tends to increase during labour, the mean of the pain score given before each period (baseline pain) and that given 20 minutes after the end of the period served as the reference value (i.e. the pain intensity when no analgesic effect was assumed) in the original studies I, II and IV. In study III, it was not possible to use the pain after the study period due to the fact that the parturients in the control group were still under the influence of the epidural block. The pain score given for the uterine contraction immediately before the study period was employed as the reference.

In studies I and III, an individual effective dose of remifentanil was defined as the last dose for each patient during which she did not want to have more effective analgesia. The time to achieve the effective dose was defined as the time elapsed from the start of the study period until the start of the first bolus dose which was deemed as the "effective" dose. In study III, the reasons given for not wanting to continue dose escalation, although the current pain score was higher

than that given by the parturient as acceptable for herself, were classed into two categories (those related to side effects such as "I'm afraid I'll fall asleep", and those related to increased tolerance to pain such as "I can still stand this pain").

The calculated averages of the NIBP, SaO_2 and HR values were included for each parturient. The SaO_2 recordings were included separately before and after the introduction of supplemental oxygen. In study II, the highest $ETCO_2$ value for each uterine contraction with PCA triggering was included in the analyses.

4.4.2 Analyses in the post hoc cohort

For the purpose of this academic dissertation, *post hoc* analyses were performed by expanding on the example of Beilin *et al.* (2003) including all parturients receiving remifentanil in the four original studies (I-IV). In study IV, the information gathered during the wash-out sequence between the study periods was disregarded. The motivation for this was to provide an overall view of the experience of the parturients who received remifentanil, while acknowledging the fact that a number of cases had been excluded from the analysis of data in the original studies in order to ascertain fair and unbiased comparisons.

This analysis of the entire cohort included the subjective scores, drug delivery data, oxygen supplementation, FHR tracing descriptions, delivery mode, UapH and Apgar scores. The conventional reference value was used in the calculation of the PID, i.e. the pain score assigned immediately before the study period. In a subgroup of parturients receiving remifentanil with a dose escalation to individual effective dose (studies I and III), the PID for the effective dose was calculated as the median of mean pain scores reported during the effective dose – the baseline pain. Other subgroups were formed to analyse variables which were not included in the protocol of all the 4 original studies or where the classification alteration or the study protocol in a particular original study would have imposed an obvious bias in the cohort analysis. Itching was included in the questionnaire in studies I and II only. The results of study II were excluded from the analysis of which factors were associated with the use of oxygen supplementation to avoid a possible bias caused by the 50% oxygen inhaled during the PCA doses. Similarly, study IV was not included in the cohort analysis of FHR changes due to a change in criteria for FHR abnormalities. Another cohort was assembled to draw together the parturients' answers as to the acceptable level of pain. This subgroup included all parturients recruited for study III (also including those randomised to EDA) and IV.

Cervical opening after the study period was used to determine the phases of 1st stage of labour due to the fact that the interval between the study period and the vaginal examination was shorter after the study period than before it. In emergency caesarean sections, the NICE classification for urgency was used (National Collaborating Centre for Women's and Children's Health 2004), but the grades of urgency II-IV were grouped together. All deviations from normal as mentioned in the obstetrician's descriptions concerning FHR tracings were included in the *post hoc* analyses. This analysis of data did not encompass data gathered with the anaesthesia monitor.

The temporal changes in pain, pain relief, sedation scores and incidence of nausea, as well as PID at various phases of labour and a scatter plot of the effective bolus doses are depicted in the figures.

4.4.3 Statistics

The numerical results were entered in SPSS 9–15 (SPSS Inc., Chicago, Illinois) and SAS (SAS, Cary, NC) software, which were used for statistical analysis. The Mann-Whitney U-, Chi Square and Fisher's exact tests were used to compare the effects of the treatments. The Wilcoxon signed ranks test was used for paired data such, as those required for the PID in studies I and III. The Spearman test was used for correlation. In the analyses of the cross-over studies, the Mann-Whitney U-test was used to ensure that the conditions for an unbiased cross-over study were met, i.e. that there was no period effect or treatment-period interaction or subsequent interaction in the comparison of the treatment effects (Altman 1991). The binomial test was used to exam the preference of medications given in study II. The differences of dichotomous variables in studies II and IV were compared with Prescott's test. P-values < 0.05 were considered as statistically significant. Data concerning patient characteristics, maternal and foetal outcomes, and details of delivery, is presented in tables. Data is presented as median (25^{th} –75^{th} percentile) if not otherwise specified.

5 Results

5.1 Patients

The main characteristics of the parturients included in the analyses are summarised in table 7. Three parturients were excluded in study I due to entering the 2nd stage of labour during the study period. In study II, the same reason resulted in excluding 2 parturients. Moreover there was one case of alarming FHR tracing prompting early termination of the study and 2 cases with technical errors (one of the parturients erroneously received both nitrous oxide and remifentanil during the study period allocated for remifentanil and one received oxygen and air during the study period for nitrous oxide) leading to the fact that only 15 were included in the analysis of the original study out of 20 recruited parturients. In study III, there were 7 excluded cases (3 in the remifentanil group due to entering the 2nd stage and 3 in the EDA group due to entering the 2nd stage and 1 in the EDA group due to dural tap). In study IV, 4 parturients were excluded due to entering the 2nd stage, 1 due to spontaneous tocolysis and 4 due to protocol violations (dose approximately + 25% during one of the two periods, due to configuration error in the infusion pump).

In the *post hoc* cohort of all those allocated to receive remifentanil, only three parturients were excluded. In study II, two parturients entered the 2nd stage of labour before the remifentanil period when only nitrous oxide had been given. In study IV, the contractions became infrequent (spontaneous tocolysis) and painless in one case while the research equipment was set up. When the parturient eventually started labour again, the PCA devices and the monitors were already in use with another case. After these exclusions, there were 114 cases in the cohort, all receiving IVPCA remifentanil.

5.2 Pain

5.2.1 Pain scores before, during and after analgesia

Pain scores and the PID in the original studies are summarised in table 8. The PID for remifentanil in study II was better than that achieved with nitrous oxide. In study III, systemic remifentanil provided weaker analgesia than epidural. There was no differences in the pain scores when the two timings of the remifentanil bolus were compared in study IV but the pain scores were higher and reciprocally the PID was smaller during the second study period (figure 1).

Table 7. Main characteristics of the parturients in the original studies I - IV and in the *post hoc* cohort. Cx = cervical dilatation, N = number of patients in the study. Data are mean (SD) range, if not otherwise specified.

Original study/ N included in analyses	Age, y	Height, cm	Weight, kg	Parity, primiparous/ multiparous, n	Medical induction of labour, n	Cx before the study, cm	Cx after the study, cm	Contraction pain score before the study (0–10)
I	27 (4)	167 (4.3)	79 (13.0)	12/5	4	3.4 (1.1)	4.6 (1.8)	7.5 (1.4)
N= 17	21 – 32	158 – 173	56 – 109			2 – 6	2 – 9	5 – 10
II	26 (6)	161 (6)	75 (10)	11/4	5	3.6 (1.2)	4.6 (1.2)	6.6 (1.8)
N = 15	16 – 34	149 – 174	63 – 98			1 – 6	2 – 7	3 – 9
III/ remifentanil N	28 (5)	166 (5.9)	79 (8.5)	17/7	7	3.9 (1.1)	6.8 (2.2)	8.5 (0.83)
= 24	22 – 39	155 – 178	62 – 92			3 – 6.5	3 – 10	7 – 10
III / epidural	28 (3)	167 (6.0)	80 (10.4)	16/5	3	4.4 (1.2)	7.0 (2.2)	8.1 (0.85)
N = 21	19 – 34	158 – 176	56 – 100			3 – 6.5	4 – 10	7 – 10
IV	28 (6)	165 (5.3)	82 (12.8)	28/13	15	2.8 (1.0)	3.9 (1.8)	6.9 (1.6)
N = 41	19 – 45	155 – 174	62 – 105			1 – 5.5	1 – 8	3 – 10
Excluded[a]	29 (4)	165 (6.4)	81 (13.4)	5/12	7	3.6 (1.0)	7.3 (3.0)	7.6 (2.1)
N= 17	23 – 38	153 – 178	60 – 109			1 – 6	1.5 – 10	3 – 10
Post hoc cohort	28 (5)	165 (5.7)	80 (11.8)	73 /41	38	3.3 (1.1)	5.2 (2.4)	7.7 (1.7)
N= 114	16 – 45	149 – 178	56 – 109			1 – 6.5	1 – 10	3 – 10

[a] receiving remifentanil

Table 8. Pain and pain relief scores in studies I – IV calculated as the mean of last score recorded every 10 minute period during the time the PCA device was available to the parturient. Data are expressed as median (25^{th} – 75^{th} percentiles).

Original study/ N included in analyses	Doses	Reference pain score (0-10)	Pain score (0-10) during analgesia	PID = Pain score during analgesia – Reference pain score	Pain relief score (0 – 4) during analgesia	Observations
I / N= 17 Open study	Remifentanil 0.2 – 0.8 µg/kg	8 (6-8.5)	4.2 (3.3-5.6)	4.2 (3.1-5.2)	2.7 (2.6-3.4)	Ref. pain = mean of pain at 0 minutes and pain 20 minutes after the study period
II / N = 15 RCT, Double blind, cross-over	Remifentanil 0.4 µg /kg	7 (6-7)	5 (3.5-7)	1.5 (1.0-3.0)	2.5 (2-3.5)	Ref. pain = mean of pain at 0 minutes and pain 20 minutes after each study period (Mann-Whitney U-test)
	Vs.					
	Nitrous oxide 50%	7 (6-8)	6.5 (6-9)	0.5 (-0.5-1) p=0.01	0.5 (0-1.5) p<0.001	
III/ N = 45 RCT, Double blind, parallel	Remifentanil 0.1 – 0.9 µ/kg	8 (8-9)	7.3 (5.6-8.2)	1.7 (0.4-2.5)	2.5 (2.2-2.9)	Ref. pain = pain at 0 minutes (Mann-Whitney U-test)
	Vs.					
	Epidural 0.0625% levobupivacaine + fentanyl 2 µ/ml	8 (7.5-9)	5.2 (2.2-6.7)	3.2 (1.3-5.3)	2.8 (2.3-3.5)	
			p=0.004	p=0.01	p=0.11	
IV/ N = 41 RCT, Double blind, cross-over[2]	Remifentanil 0.4 µg/kg					Reference pain for period 1: pain at 0 minutes Reference pain for period 2: mean of pain at 0 minutes and pain 20 minutes after the study period [a] (Mann-Whitney U-test)
	1^{st} period					
	group 1	7.2 (6.3-8.0)	4 (2.8-5.1)	2.5 (1.9-4.1)	3 (2.9-3.5)	
	group 2	7.0 (5.3-7.5)	3 (2-4.3)	3.3 (2.3-5.0)	3.3 (3.0-3.5)	
			p=0.116	p=0.388	p=0.544	
	2^{nd} period					
	group 1	7.7 (6.5-8.5)	4.8 (3.3-6.4)	2.5 (1.2-3.6)	3 (2.5-3.5)	
	group 2	7.7 (6.5-8.5)	5.3 (4.0-6.0)	2.3 (1.3-3.2)	3 (2.0-3.5)	
			p=0.948	p=0.724	p=0.661	

[a] The pain score before the 1^{st} study period: the mean pain score of three consecutive contractions before the 1^{st} study period.

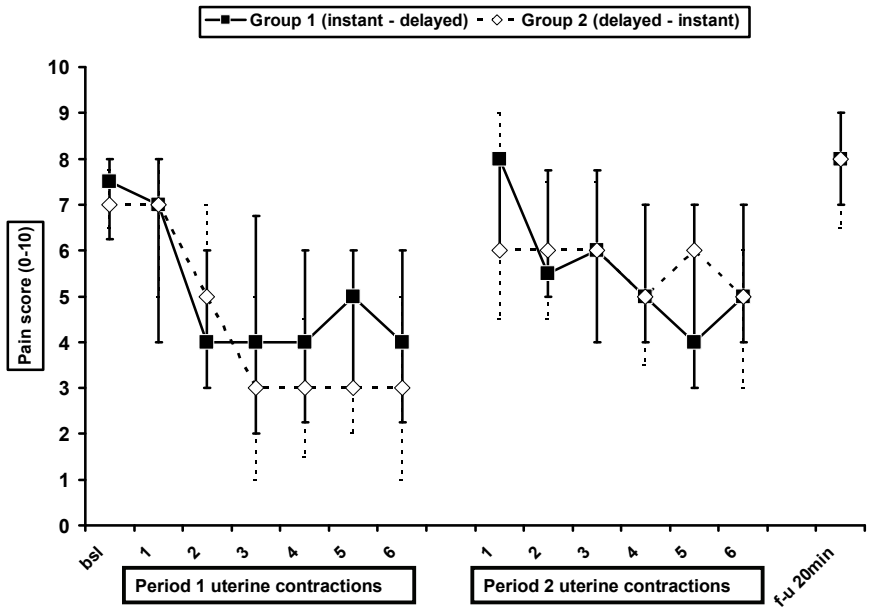

Fig. 1. Pain scores (median ± 25th and 75th percentiles) after each of the first six uterine contraction during two study periods in a cross-over study. Group 1 (n = 22) received PCA bolus during the uterine contractions (instant) during the first period and between uterine contractions (delayed) during the second. Group2 (n = 19) received the medication in opposite order. bsl = pain before the study, f-u 20 min = last pain score given before 20 minutes elapsed of the follow-up time with no medication.

In a subgroup of 19 parturients with a stable uterine contraction interval, and excess bad demands compensated, however, there was a small difference in the PID in favour of the delayed bolus. It should be noted that in the original studies I, II and IV, the PID was calculated using a reference pain which takes the natural increase in labour pain as labour progresses into account.

In the *post hoc* cohort, a statistically significant ($p < 0.001$) reduction of pain (compared with the pain at baseline) was noted at all time points 10–60 minute (Fig 2). There was a trend towards higher pain scores at 70 minute at which time point the pain scores were not different from the pain scores at the baseline. The number of parturients continuing the study was markedly reduced, however, at this time point. The median pain score during remifentanil analgesia was 5 (3.5 –

7) which was significantly lower than the baseline pain ($p < 0.001$, Wilcoxon signed ranks test). The PID was 2 (0.7–3.7). After the study period, pain scores exceeded the baseline pain by 20 minutes. Only 46 women (40%) achieved a clinically significant reduction in pain (at least 33% decrease from the baseline pain) as determined by *Farrar et al.* (2000).

The PID was 2.1 (1.4–4.1), 1.8 (0.5–2.8) and 2 (0.1–4.7) during the latent, active and transitional phases of labour, respectively (figure 3) with no difference ($p > 0.05$, Mann-Whitney U-test) between the phases. It was not influenced by age, weight or whether labour was induced or spontaneous.

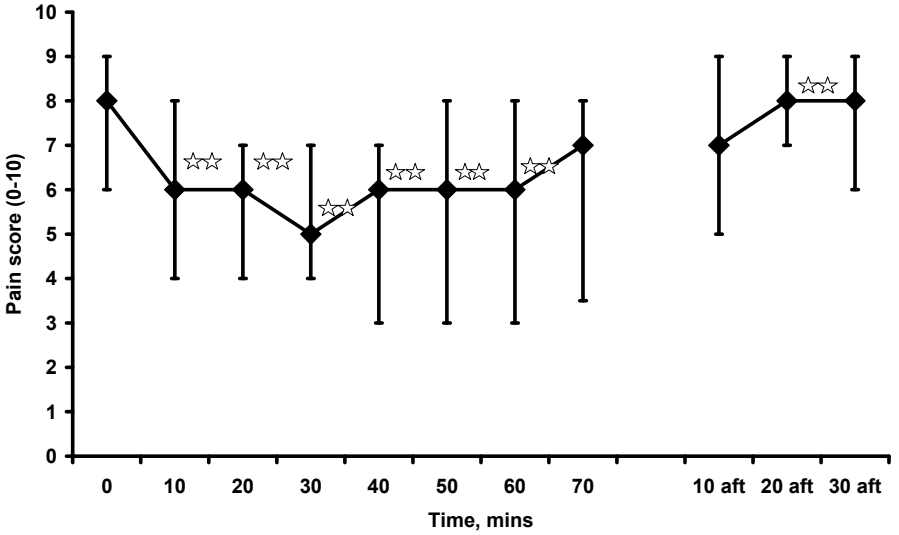

Fig. 2. Pain scores (median ± 25th and 75th percentiles) during remifentanil analgesia and during the follow-up sequence with no analgesia. Respondents were 114, 113, 109, 94, 89, 77, 68 and 11 at 0, 10, 20, 30, 40, 50, 60 and 70 minutes, respectively. After the study period 92, 91 and 28 parturients' responses were recorded at 10, 20 and 30 minutes, respectively (10–30 aft). The study period exceeded 70 minutes in 7 cases with pain score of 6 (5–7.25). ($p < 0.001$ in comparison with the baseline pain, Wilcoxon signed ranks test)**

There seemed to be no correlation between the PID and the consumption of remifentanil ($p = 0.474$, Spearman test), but the PID was higher in the open study

design (study I) compared with RCTs (studies II-IV) and marginally higher with parturients in studies I and III using the individually titrated dose, as compared to those in studies II and IV, which employed fixed doses (table 9). There was a significant difference between the PID in study I compared with that of studies II and IV using a fixed dose ($p < 0.001$).

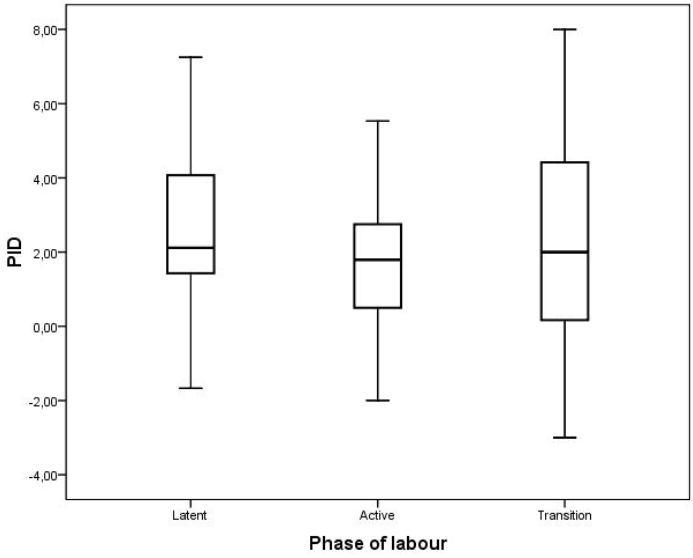

Fig. 3. PID (median ± 25th and 75th percentiles) at different phases of labour. Data from 52, 44 and 16 parturients at latent (Cx≤4 cm), active (Cx>4cm and ≤ 8cm) or transitional phase (Cx>8cm) of labour at the end of the study period.

In the *post hoc* cohort, the analysis of the data concerning those parturients participating in studies with a dose escalation up to an individual effective dose (studies I and III) indicated that the mean pain score after the efficient dose had been reached was 4.6 (2.5 – 6) with a reduction of 3.5 (2–4.9) compared with the baseline pain. The PID at the effective dose was 4.2 (2.2 – 5) in study I and 3.5 (1.6–4) in study III ($p < 0.001$, Mann-Whitney U-test). The PID in this subgroup of 34 out of 47 parturients reaching the effective dose seemed not to be influenced by parity (primipara vs. multipara, $p = 0.639$, Mann-Whitney U-test), or whether the labour was induced ($p = 0.557$, Mann-Whitney U-test). The PID did not appear to be correlated with the efficient bolus doses or the consumption of remifentanil during the efficient doses ($p = 0.768$ and 0.903, respectively, Spearman test).

Table 9. PID during remifentanil analgesia and potentially influencing factors. Mann-Whitney U-test.

	Yes	No	p-value
Accompanying person	1.83 (0.5 – 2.63)	1.5 (0.5-2.0)	0.223
	n=83	n=11	
Antenatal classes	1.8 (0.5-2.5)	1.9 (0.3-3.9)	0.783
	n=79	n=12	
Primipara	2 (1-3.8)	2 (0.5-3.7)	0.639
	n=73	n=41	
Induced labour	2 (0.5-3)	2(0.7-3.9)	0.557
	n=38	n=74	
Fixed dose	1.8 (0.5 – 2.6)	2.5 (0.8 – 4.5)	0.025
	n=67	n=47	
RCT	1.8 (0.5 – 2.5)	4.5 (3.5 – 6.1)	<0.001
	n=94	n=20	

5.2.2 Acceptable pain

In studies III and IV, parturients receiving remifentanil (n = 74) and the epidural group in study III (n = 22) provided the pain scores they thought would be acceptable during the current labour. This was 4 (3-5) with no difference according to parity (p = 0.644, chi^2, figure 4).

5.3 Pain relief and satisfaction with analgesia

In study I, pain relief scores given by the parturient during analgesia were compared with the pain relief score given 20 minutes after cessation of remifentanil analgesia when no analgesics were given. The difference was 2.7 (1.7–3.6) (p < 0.001, Mann-Whitney U-test) which is not different from the mean pain relief score during analgesia (table 8). All women completing the study would have liked to continue with remifentanil IVPCA if this had also been available after the study period.

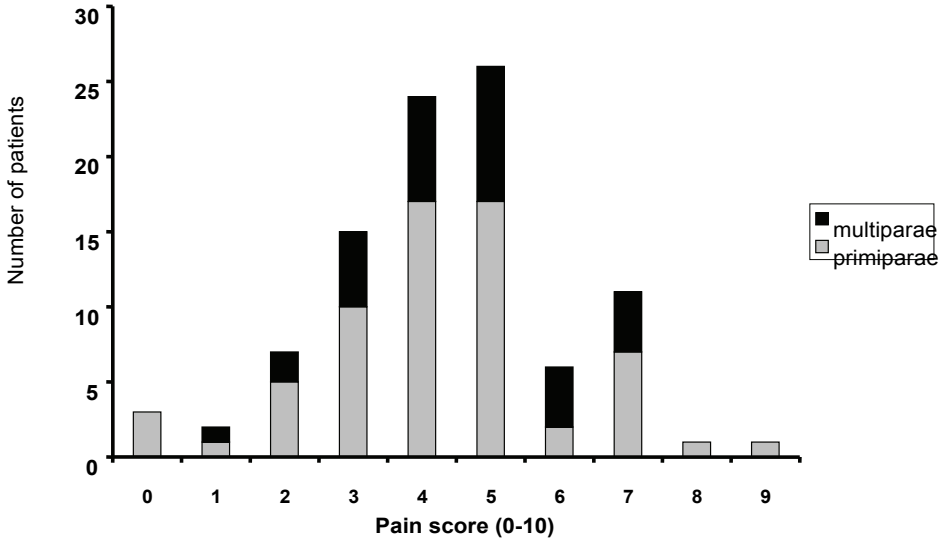

Fig. 4. Answers of 96 parturients in active labour to the question: "Which pain score would you find acceptable during this labour".

Pain relief score during remifentanil analgesia was 2.5 (2–3.5) which was higher than that given during nitrous oxide 0.5 (0–1.5) ($p < 0.001$, Mann-Whitney U-test) in study II. Thirteen parturients would have continued with remifentanil and 3 would have continued with nitrous oxide ($p = 0.0056$, Prescott's test). Most parturients preferred remifentanil to nitrous oxide (14 vs. 1) ($p = 0.02$, binomial test).

Although there was a clear difference in pain scores between remifentanil IVPCA and EDA, the pain relief scores were similar (table 8). Nineteen (86%) out of 22 in the remifentanil group and 17 (85%) out of 20 receiving EDA would have liked to continue with the given medication if it were in routine use ($p = 1.0$, chi^2 test). Two and 4 parturients in the remifentanil and epidural groups, respectively, had their study period discontinued due to a failure to reach an efficient level of analgesia during dose escalation of IVPCA medication (which was either remifentanil or placebo).

In study IV, there was a period effect with a better pain relief score, 3 (3.0–3.5), for the first study period compared with 3 (2.0–3.5) for the second period ($p = 0.009$, Wilcoxon signed ranks test). When the study periods were analysed separately comparing the groups as in parallel studies, there was no difference in

pain relief scores or in the proportion of parturients willing to continue with the method used.

In the *post hoc* cohort, the mean pain relief score was 2.7 (2.2–3) in the entire group of 114 parturients receiving remifentanil with 16 (14%) parturients reporting a mean pain relief score of less than 2 (corresponding to no or slight pain relief) during analgesia with no influence by the study design. Ninety nine (90%) of 110 responders would have continued with remifentanil analgesia when the first period of study IV was included in addition to the participants in studies I-III. When the second period in study IV was also considered, the negative answers increased by 9, making the overall proportion of parturients willing to continue with remifentanil 86 (81%) out of 106.

5.4 Doses of PCA with remifentanil and intermittently inhaled nitrous oxide

In study I, all 17 parturients included in the analysis achieved an individual effective dose (a dose after which they did not want to increase the efficacy of analgesia). The median time for reaching the individual effective dose was 21 (0–31) minutes. In study III, fifteen (63%) out of 24 patients receiving remifentanil and 13 (62%) out of 21 receiving epidural analgesia reached the effective dose during the study period ($p = 1.0$, chi^2 test). The median time for achieving the individual effective dose was 40 (19–51) minutes in the remifentanil group and 10 (0–29) minutes in the epidural group ($p = 0.006$, Mann-Whitney U-test)).

In study IV, there was a larger consumption of remifentanil during the second study period ($p = 0.007$, Wilcoxon signed ranks test).

In the *post hoc* cohort analysis, the parturients received a total dose of 196 (149–333) µg during the study period of 38 (24–61) minutes ranging from 10 to 73 minutes, during which remifentanil was available for the parturients. The consumption of remifentanil was 0.07 (0.06–0.1) µg/ kg/min. The parturients using the fixed dose of 0.4 µg/kg consumed remifentanil at a rate of 0.07 (0.06–0.09) µg/kg/min and those with the individually titrated dose 0.08 (0.06–0.12) µg/kg/min ($P = 0.30$, Mann-Whitney U-test). There was a correlation between mean pain scores during the analgesia and the consumption of remifentanil ($p = 0.035$, Spearman test)

In the *post hoc* cohort, the analysis of the data from studies I and III indicated that 19 out of 20 parturients in study I and 15 out of 27 in study III achieved the effective dose. Reasons for not reaching the effective dose were: 4 did not have

time enough to go through the titration due to entering into the 2nd stage of labour, 3 could not go through the whole dose escalation within the given time, 1 stopped the study earlier than planned due to side effects and 5 found the preset maximum dose of 0.8 - 0.9 µg/kg ineffective. It took 22 minutes (9–42) for the parturients to reach the effective dose during the dose escalation. The open study design was associated with a faster escalation to the effective dose which was reached by 13 (0–30) minutes in study I vs. 40 (20–52) minutes in study III (p = 0.006, Mann-Whitney U-test). The individual effective dose was determined to be 0.4 (0.2–0.6) µg/kg with a minimum of 0.2 µg/kg and a maximum 0.9 µg/kg. In study I, the effective bolus was 0.4 (0.2–0.4) µg/kg, and in III, 0.5 (0.3–0.7) µg/kg (p = 0.065, Mann-Whitney U-test). The lowest starting dose of 0.1µg/kg in study III was deemed inadequate by all. There seemed to be a correlation between the effective PCA bolus and baseline pain (Figure 5), but no correlation was found between the effective dose and the PID reached with the effective dose (p = 0.467, Spearman test). There seemed to be a trend towards parturients in the transitional phase reaching an effective analgesia with a larger bolus compared with the parturients in the earlier phases of labour (0.65µg/kg, 0.28–0.85µg/kg Vs. 0.4 µg/kg, 0.2–0.49µg/kg, respectively) (p = 0.061, Mann-Whitney U-test).

The consumption of remifentanil during the effective dose was 0.085 µg/kg/min (0.068–0.15µg/kg/min) with a range from 0.03 to 0.32 µg/kg/min. The parturients receiving remifentanil in study III consumed 0.14 (0.08–0.18) µg/kg/min at the effective dose which was twice as much as the consumption in the open study (P = 0.035, Mann-Whitney U-test). There was a correlation between the consumption of remifentanil and the baseline pain with a Spearman coefficient of 0.46 (p = 0.006), but again there was no correlation between the consumption of remifentanil and the reduction in pain score (p = 0.447, Spearman test). The parturients in the transitional phase seemed to reach an effective analgesia with a larger consumption of remifentanil compared with parturients in the earlier phases of labour (0.17 µg/kg/min, 0.083–0.21µg/kg Vs. 0.08 µg/kg, 0.06–0.13 µg/kg) (p = 0.033, Mann-Whitney U-test).

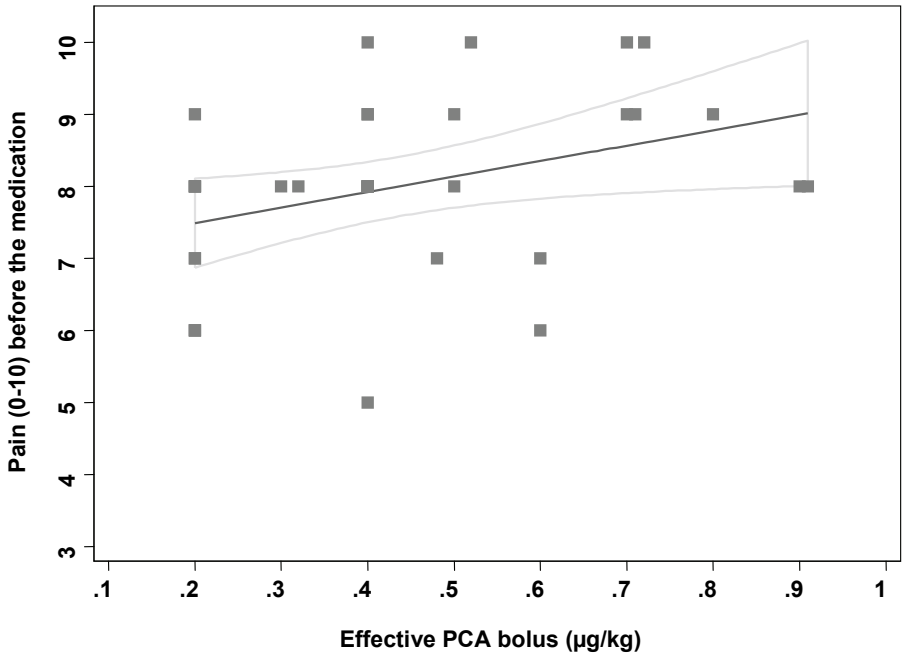

Fig. 5. Scatter plot on pain at the baseline and dose. The thick line represents the regression coefficient (b = 2.2, P = 0.017) while the thinner lines the 95% confidence interval (95% CI).

In study II, the highest concentration of FiN_2O was 49% (45—52%) during the PCA boluses of the N_2O periods. The highest ETN_2O value was 30% (22—36%). The lowest FiO_2 value was 47% (45–53%) during remifentanil and 48% (44–53%) during N_2O ($p = 0.7$, Mann-Whitney U-test). The proportion of contractions for which the parturients triggered PCA signals was 0.9 (0.7–1.0) for remifentanil and 1.0 (0.9–1.0) for N_2O ($p = 0.3$, Mann-Whitney U-test). Altogether, the parturients spent 260 (165–318) s breathing through the mask during nitrous oxide periods compared to 170 (107–275) s during remifentanil periods ($p = 0.045$, Mann-Whitney U-test).

5.5 Side effects

5.5.1 Respiratory effects

In study I, the respiratory rate during the analgesia among 14 parturients (for whom this variable had been recorded) was 11 (9.8–15.3) with no difference from baseline (p = 0.683, Wilcoxon signed ranks test).

In study II, there were two parturients with short periods (< 60 s) of desaturation < 95%, one of whom desaturated during both study periods and one who desaturated only during remifentanil medication. The mean highest $ETCO_2$ during the contractions with remifentanil was 3.9 (3.2–4.3) while it was 3.7 (3.5–3.9) during nitrous oxide (p = 0.06, Mann-Whitney U-test). The SaO_2 was 98% (97.1–99%) during the remifentanil periods and 98.8% (98.5–99.3%) during the study periods with nitrous oxide (p = 0.001, Mann-Whitney U-test).

Oxygen supplementation was given to 13 out of 24 (54%) among those receiving remifentanil analgesia while only one parturient needed oxygen supplementation in the epidural group of 21 parturients in study III. There were two parturients with desaturation < 95% lasting for > 1 minute in spite of oxygen supplementation.

In study IV, a similar proportion of 9 out of 41 needed oxygen supplementation during both of the different ways to time remifentanil bolus during IVPCA. Among those with no oxygen supplementation, the mean SaO_2 during the contractions 4–6 was 97.6 (96.6–98.4) during the immediate bolus while it was 97.8 (96.9–98.3) during the delayed bolus (p = 0.273, Mann-Whitney U-test)

The *post hoc* analysis of 96 cases in studies I, III and IV revealed that there were 32 parturients (33%) given oxygen supplementation during the remifentanil analgesia due to SaO_2 showing desaturation below 94–95%. There was a trend towards a greater need for oxygen supplementation in the RCTs than in the open study (p = 0.064, Fisher's Exact test), but this did not make any difference with respect to whether a fixed dose was employed (p = 0.312, Chi-square test). Table 10 lists the variables tested for an association with the need for oxygen supplementation.

During the dose escalation among 17 parturients requiring oxygen supplementation in the subgroup of parturients in studies I and III in the *post hoc* cohort, the need for oxygen supplementation arose when the PCA bolus was 43 (30–58) µg with a minimum of 24 µg corresponding to dose of 0.6 (0.4–0.7)

µg/kg with a minimum of 0.3 µg/kg. Women with oxygen supplementation reached the effective dose at a higher level than those who did not need oxygen supplementation (table 11). In this small group of parturients there was no association between baseline pain or pain during analgesia and the need for oxygen supplementation. The open study design was associated with less oxygen supplementation (p = 0.03, Fisher's Exact test).

Table 10. Variables related to the need for oxygen supplementation in studies I, II and IV in the *post hoc* cohort. Mann-Whitney U-test. Data are expressed as median (25^{th} – 75^{th} percentiles).

Variable	O_2 supplement n=32	No O_2 supplement, n= 64	p-value
Weight	85.5 (75 – 92)	76.25 (70 – 87.8)	0.03
BMI	30.2 (28.3 – 33.9)	28.7 (25.8 – 31.8)	0.04
Height	165 (162-170)	165 (162-170)	0.988
Age	27 (25– 32)	27.5 (24.3 – 31.8)	0.785
Pain at baseline	8 (6.8 – 9)	7.7 (6.4 – 8.0)	0.117
Average pain during analgesia	6.3 (3.8 – 8.0)	4.7 (2.9 – 6.3)	0.030
PID	1.5 (0.5 -2.9)	2.2 (1.5 – 4.2)	0.065
Sedation score	2.4 (1.8 – 2.7)	1 (0.7 – 2.2)	<0.001
Remifentanil consumption µg/kg/min	0.09 (0.066 – 0.12)	0.067 (0.05 – 0.089)	0.002

Table 11. Variables related to the need for oxygen supplementation among those reaching the effective dose (studies I and III in the *post hoc* cohort). Mann-Whitney U-test. Data are expressed as median (25^{th}–75^{th} percentiles).

Variable	O_2 supplement n=11	No O_2 supplement, n= 23	p-value
Pain at baseline	8 (6.8 – 9)	7.7 (6.4 – 8)	0.117
Pain during the effective dose	5.3 (2.5 – 7.5)	3.8 (2.4 – 5.6)	0.277
Effective bolus, µg	39 (30 – 60)	28 (18 – 36)	0.017
Effective bolus, µg/kg	0.6 (0.4 – 0.72)	0.4 (0.2 – 0.4)	0.016
Remifentanil consumption at effective dose µg/kg/min	0.15 (0.09 – 0.18)	0.07 (0.05 – 0.1)	0.006

5.5.2 Sedation and dizziness

In study II, parturients scored sedation during remifentanil analgesia as 2 (1.5–2.5) and during nitrous oxide as 0.5 (0–1.5) (p = 0.001, Mann-Whitney U-test). There was an even more clear difference in sedation scores when remifentanil analgesia was compared with epidural analgesia in study III: 2.3 (1.3–2.6) and 0 (0–0.8), respectively (p<0.001, Mann-Whitney U-test). In this study, seventeen and seven

parturients in the remifentanil and epidural groups, respectively, gave reasons for not increasing the dose even though the pain was higher than the acceptable pain. The reason was related to side effects in seven cases (five fear of increased sedation and two dizziness) receiving remifentanil, while side effects were not the reason in the group of epidural analgesia.

In study IV, there was a trend towards stronger sedation when the PCA bolus was given immediately following the PCA trigger by the parturient compared with the sedation scores given during the delayed boluses: 2 (1–3) and 2 (0.75–3), respectively, but this finding was not statistically significant ($p = 0.061$, Mann-Whitney U-test).

In the *post hoc* cohort, the sedation score during remifentanil analgesia was 1.8 (1–2.5) on a subjective scale (0 = no sedation, 1 = slight sedation, 2 = modest sedation and 3 = strong sedation). The temporal pattern of sedation during the time that the PCA with remifentanil was available to the parturients is depicted in figure 6.

In spite of some parturients reporting a strong sedation, none of them lost consciousness and all parturients were able to respond verbally to the questions included in the protocol. A correlation seemed to exist between the consumption of remifentanil and sedation, with a correlation coefficient of 0.3 ($p = 0.001$, Spearman test). The sedation score was 1 (0.8–1) during the open study and 2 (1–2.5) in the RCTs ($p < 0.001$, Mann-Whitney U-test), while there was a trend towards more sedation when a fixed dose was employed.

Dizziness was specifically and spontaneously reported by 24 parturients. The consumption of remifentanil was 0.066 (0.058–0.097) and 0.076 (0.059–0.10) among those reporting dizziness and those not reporting it, respectively ($p = 0.2$, Mann-Whitney U-test).

5.5.3 Nausea, vomiting and other maternal side effects

In the study comparing remifentanil with nitrous oxide (study II), five and six parturients scored nausea > 0 during N_2O and remifentanil, respectively. The score (0–10) of nausea was 0 (0–2) for both medications ($P = 0.8$, Mann-Whitney U-test). One patient who preferred N_2O spontaneously reported her preference to be due to the more severe nausea during the remifentanil period.

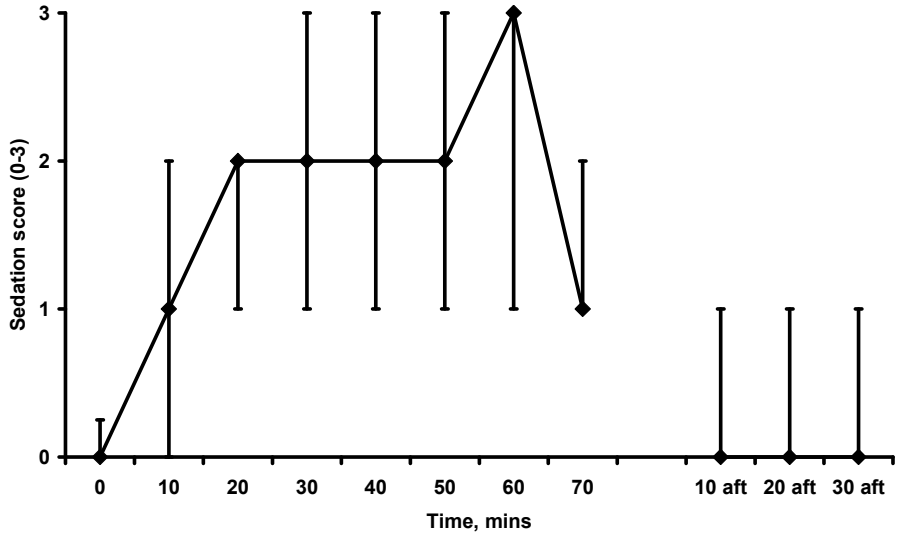

Fig. 6. Median sedation scores (25%-75%) during remifentanil exposure and during the follow-up sequence with no analgesia. Respondents were 107, 103, 87, 85, 72, 63 and 9 at 0, 10, 20, 30, 40, 50, 60 and 70 minutes, respectively. After the study period 81, 79 and 20 parturients' responses were recorded at 10, 20 and 30 minutes, respectively (10 - 30 aft).

When remifentanil was compared with epidural analgesia (study III), the number of parturients with nausea was larger in the remifentanil group both before the study and during the medications. An *ad hoc* analysis revealed a decrease in nausea scores during the study period compared with baseline values in the remifentanil group ($p < 0.04$, Wilcoxon signed ranks test). Three parturients vomited during the study period. All of them received remifentanil.

In study IV, there were 11 parturients (18%) with nausea and none vomited during baseline observation lasting for 3 contraction cycles. Seven (14%) and 13 (28%) parturients reported nausea during the contraction cycles 4 – 6 of the first and the second study period, respectively. Vomiting was observed in 4 cases out of 49 during the contraction cycles 4–6 of the first period and in 6 cases of the 47 parturients at the contractions 4–6 of the 2nd period, while no vomiting was observed during the observation at baseline.

In the *post hoc* cohort, out of 112 parturients who responded to a question of nausea at baseline, nausea (nausea score > 0) was reported by 28 (25%). Thirty-four (30%) reported nausea (nausea score > 0) at least once during the study period when IVPCA remifentanil was available. During the follow-up time, nausea scores were given by ninety nine parturients out of which 27 (24%) were positive. Figure 7 displays the proportion of parturients with nausea at separate time points.

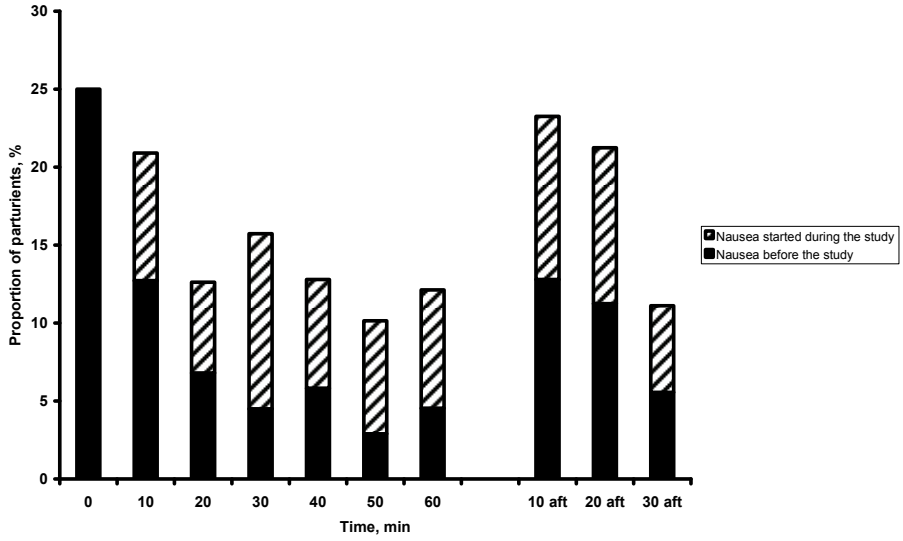

Fig. 7. Proportion of parturients with nausea during remifentanil exposure and during the follow-up time at separate recording times. The number of respondents varied according to end of the study period and availability of parturients' assessments: 112, 110, 103,89,86,69 and 66 at 0,10,20,30, 40, 50 and 60 minutes. After the study period responses were recorded from 86, 80 and 18 at 10, 20 and 30 minutes (10–30 aft).

Nausea before any remifentanil had been given seemed to be the most powerful predictor of whether nausea was observed during remifentanil exposure. Fifteen of the 28 women with nausea before the study also reported nausea during exposure ($p = 0.002$, chi^2 test). A history of motion sickness, and previous experience of PONV served also as predictors of nausea during remifentanil analgesia ($p = 0.012$ and 0.06, respective, chi^2 test). Out of the 15 regular smokers, 2 reported nausea during remifentanil analgesia ($p = 0.13$, Fisher's exact test).

The PID was 1.5 (0.5–2.4) in the subgroup with nausea while those without nausea had a PID of 2.1 (1.3–4.2) ($p = 0.017$, Mann-Whitney U-test). There was a trend towards higher pain scores among those with nausea ($p = 0.07$, Mann Whitney U-test). None of the other tested variables (age, height, weight, BMI, cervical opening, consumption of remifentanil, parity, drug delivery method, induction of labour, use of oxytocin, pain at the baseline and study design) were associated with difference in this regard.

Twenty parturients had a higher mean nausea score during remifentanil analgesia than before it. The PID was 1.1 (0.5–2.1) among them while it was 2 (1.3–4.1) among those whose nausea score did not increase with analgesia ($p = 0.018$, Mann-Whitney U-test). With regards study design, employing a fixed dose and RCT were associated with whether nausea became more severe after starting the remifentanil PCA ($p = 0.021$ and $p = 0.011$, respectively, Chi-square test). None of the other tested variables (parity, age, height, weight, BMI, Mean of pain scores during the analgesia, consumption of remifentanil, history of motion sickness, previous PONV and smoking) were different with respect to an increase in the nausea score. Among the 28 parturients who had nausea before the study medication was started, the average nausea score during remifentanil exposure was higher than the baseline score in only one case. There was a decrease in the nausea score from baseline in 25 cases.

Vomiting during remifentanil analgesia was noted in 11 cases (10%) in the entire cohort and in 8 cases (8%) of those 102 parturients of whom there was a record of the follow-up time.

Out of the 38 parturients receiving remifentanil during studies I and II, 10 reported itching.[1] This was scored as "weak" by 8 women. One parturient scored itching as "modest" and one as "strong". The itching classified as strong was localised at the nose. Only one parturient had itching (classified as weak) during the nitrous oxide period in study II.

In study I and IV, three parturients reported difficulty in reading and visual focusing, and one of them had difficulty in swallowing. During all the studies, it was not uncommon that there was a brief episode of shivering shortly after the cessation of analgesia.

No maternal bradycardia (HR < 50 bpm) or hypotension (SAP < 90mmHg) was observed during remifentanil analgesia during the four original studies.

[1] Itching was reported at one or both of the time points of recording by 5 parturients in study I and 5 in study II (instead of 2 reported erroneously in the original paper).

Maternal HR was 88 (75–99) and 87 (79–96) during remifentanil and nitrous oxide (p = 0.2), the respective values for MAP were 96 (88–110) mmHg and 96 (91–107) mmHg (p = 0.3) in study II. Similarly, no difference was seen in haemodynamic parameters during remifentanil analgesia compared with EDA (study III). In study IV, the two ways of timing the remifentanil bolus were not associated with significant differences concerning heart rate or blood pressure.

5.6 FHR tracings, delivery mode, UapH and Apgar scores

The proportions of suspicious or pathological FHR tracings according to NICE (2001) guidelines (studies I-III) and a later 2007 guideline (study IV) during remifentanil administration in the original studies are listed in table 12 (National Collaborating Centre for Women's and Children's Health 2007). In study I, four patients had reduced beat-to-beat variability alone or combined with early decelerations, and one patient had early decelerations. In study II, the FHR tracing was observed as having reduced beat-to-beat variability in three cases during remifentanil administration. There was one case with early decelerations and two cases with reduced beat-to-beat variability during N_2O. All three instances of abnormal FHR tracings during N_2O were noted during the first study period excluding the possibility that the FHR abnormality would have been due to a carry-over effect. In study III, pathological tracings were noted in 9 / 24 and 7 / 19 cases in the remifentanil and EDA groups, respectively (p = 0.965, chi^2 test).[2] The proportions of tracings with deviations from the normal in the obstetrician's descriptions were 13 / 24 and 9 / 19, respectively (p = 0.736, chi^2 test). In study IV, there was only one case with an abnormal tracing according to the NICE criteria among those included in the analyses of the data. This woman had a non-reassuring electronic foetal heart rate monitoring (EFM) 10 minutes before and during the first period with absent variability. During the pause before the second period the EFM became abnormal with absent variability and variable decelerations, and continued to be abnormal over the second period. Sixteen minutes after finishing the second period the EFM became normal.

Descriptions by the obstetrician concerning 65 FHR tracings were available for retrieval for the *post hoc* cohort of cases in studies I, II and III. Twenty two of the tracings included the following abnormalities during remifentanil analgesia: Decreased microvariability in 10, missing accelerations or missing

[2] The published report of study III includes a typing error regarding abnormal FHR tracings in table 2.

macrovariability in 4, sinusoidal pattern in 2, early decelerations in 4, variable decelerations in 2, and late decelerations in 6 cases. Out of these 22 cases with abnormal tracings during analgesia, there was a report submitted by the obstetrician concerning the FHR tracing immediately before the study period in 5 cases and in 18 cases during the follow-up period indicating that in 15 cases the abnormality had either started during the remifentanil analgesia or it subsided soon after the analgesia was stopped. In 4 cases there was no statement by the obstetrician concerning the tracing before or after the study period. Study design (open vs. RCT) did not have an effect on this variable ($p = 0.218$, Chi-square test). According to the anecdotal records available to the research, foetal capillary blood samples were taken soon after the study period in two cases.

In the subgroup of the *post hoc* cohort including studies I and III which employed a dose escalation, the individual effective bolus dose was 0.51 (0.34–0.70) µg/kg and 0.4 (0.2–0.49) µg/kg among those with and without FHR abnormalities, respectively ($p = 0.12$, Mann Whitney U-test). However, the consumption of remifentanil during the individual effective dose was 0.17 (0.08–0.21) µg/kg/min vs. 0.08 (0.05–0.10) µg/kg/min among those with and without FHR abnormalities, respectively ($p = 0.007$, Mann Whitney U-test). The occurrence of a FHR abnormality was not associated with a need for oxygen supplementation in the same subgroup ($p = 0.226$, chi^2 test).

The details concerning delivery in the individual studies and in the post *hoc cohort* are summarised in table 12. Among the 114 parturients receiving remifentanil analgesia, the deliveries took place 3 hours 31 minutes (2:07–6:19) after the end of the last remifentanil bolus. There were five deliveries with a grade 1 emergency caesarean section which took place 19 minutes – 11 hours 40 minutes after the end of the last bolus of remifentanil. One of these was performed when there was a sudden prolonged deceleration in a situation where the parturient was using remifentanil after the follow-up time. In grade 2–4 emergency caesarean sections and in the vacuum extractions this interval was 2 hours 25 minutes–21 hours 14 minutes and 1 hour 30 minutes – 8 hours 26 minutes, respectively.

In the subgroup of 9 cases with a short (< 30 minute) interval between the end of the last dose to delivery, the consumption of remifentanil, Apgar score at 1 minute / 5 minute and the UapH were comparable with values recorded among parturients from the entire cohort (table 12).

Table 12. FHR, delivery mode and neonatal outcome in the original studies (I-IV) and in the compiled analysis of the 114 parturients receiving remifentanil analgesia during labour. CS = caesarean section, R = remifentanil, N_2O = 50% nitrous oxide in oxygen, EDA = epidural analgesia. N = total number of parturients in the study, n = number of events. Data are median (25^{th}–75^{th} percentile) if not specified other.

Original study/ N included in analyses	Abnormal (I-II) or pathological (III-IV) FHR (n/N)	CS/ ventouse (n)	Apgar, median (range) 1 minute / 5 minute	UapH (range)
I / N= 17 Open study	5 / 17	1/2	9 (6-9) / 9 (7-10	7.17 (7.04-7.32)
II / N = 15 RCT, Double blinded, cross-over	R 3 / 15 N_2O 3 / 15	2/2	9 (6-9) / 9 (6-10)	7.21 (7.06-7.36)
III/ N = 45 RCT, Double blinded, parallel R 24, EDA 21	R 9 / 24 EDA 7 /19[a]	R 1 /4 EDA 1 / 1	R 9 (6-10) / 9 (8-10) EDA 9 (8-9) / 9 (9-10)	R 7.25 (7.02–7.36) EDA 7.21 (7.03–7.33)
IV/ N = 41 RCT, Double blinded, cross-over	1 / 41	5 / 5	9 (4 -10)/ 9 (6-10)	7.23 (7.07 – 7.43)
The *post hoc* cohort N = 114	25 / 113[b]	13 / 13	9 (2-10) / 9 (5-10)	7.22 (7.02 – 7.43)
Short last dose to delivery –time N = 9	2/8 [a]	1 / 0	9 (8-10) / 9 (9-10)	7.24 (7.12 -7.37)

[a] Two descriptions of FHR tracing missing. The published report of study III includes a typing error regarding abnormal FHR tracings in table 2

[b] One description of FHR tracing missing

6 Discussion

6.1 Pain scores and pain relief scores

The main finding of the current investigation is that IVPCA with remifentanil is a valid method for the relief of labour pain. With the drug delivery method used in the current study, the parturients were able to obtain a reduction in pain scores by a median of 2 units on a VRS 1–10. The PID achieved with remifentanil is within the range of reduction in pain scores for the initial hour of analgesia in the other clinical studies concerning remifentanil (table 1). It was not affected by parity or phase of labour or any other maternal factor included in the *post hoc* analysis. Hence it may be difficult to propose any particular group of parturients who would especially benefit from IVPCA remifentanil analgesia during labour. A number of variables were excluded from the scope of the current study, however, which could potentially make a difference in whether remifentanil analgesia will be successful in a parturient or not. The most important topic for future studies would likely be to determine whether different genotypes concerning the structure of the μ-receptor affect the outcome. In studies regarding intrathecal fentanyl, the ED_{50} established with a sequential allocation method displays a 1.5 fold difference in relationship with the presence of a certain genotype (Landau *et al.* 2008).

It appears that the study type had the strongest association with the PID reached in the original studies. The best pain reduction was noted in the first study which was open and nonrandomised. There was also a small difference favouring individual titration (studies I and III) instead of a fixed dose (studies II and IV). There was a clear difference in the PID at the effective doses depending on the study type with a more effective analgesia in the open study compared with the RCT in which EDA was used in the control group.

There are at least two explanations for the large variation in PID between the individual studies and study designs. It is probably not uncommon to find that the response recorded in an open study cannot be replicated in a randomised, double-blinded, controlled trial. Perhaps the researchers' enthusiasm with the open design has some influence on the parturients pain ratings. The parturients consenting to participate in the first study when there were no reported systematic studies may have influenced the exceptional compliance with the study medication.

Alternatively the pain in study III might have been more resistant than the pain observed in study I for a reason which could not be revealed in the current investigation. This scenario could be explained with the definitions suggested by Akerman & Dresner (2009) in which the 'primary breakthrough pain' refers to the moment when a woman first requests analgesia during labour which is often managed with less invasive methods. 'Secondary breakthrough pain' is used when the analgesia used previously becomes ineffective. In the current investigation, the study designs probably selected more parturients in the situation of primary breakthrough pain in studies I, II and IV. The fact that study III required an epidural catheter could have caused a bias with more parturients in secondary breakthrough pain. In this scenario, the poorer response in the two studies employing a fixed dose would not solely be a result of a bias but rather should be considered as a clinically meaningful difference. The difference between the median PID of 4.5 and 1.8 in study I (with dose escalation) and the combined result in studies II and IV (with fixed dose) would be in accordance with the difference in results observed between those in a study employing the dose escalation as reported by Evron *et al.* (2005) on analgesia during the 1st hour, and those reported by Volikas and Male (2001), Thurlow *et al.* (2002), Volikas *et al.* (2005) and Blain *et al.* (2005) in their studies employing fixed doses (table 1).

It is important to know to which extent parturients wish labour pain to be reduced. In studies III and IV, the parturients expressed a pain score which they regarded as acceptable during the current labour before commencement of the study medication. This acceptable pain score was somewhat higher than what has traditionally been regarded as the cut-off point for successful analgesia (figure 4). It is possible that the parturients recruited in these studies represent an exceptional population from which the results cannot be applied to the general population of parturients requesting pain relief. Indeed, the acceptable pain score in the current sample was higher than the pain score reported by parturients needing additional medication after an epidural block (Beilin *et al.* 2003). If a pain score as high as 4 is also acceptable in other populations of parturients, however, this should be taken into account in planning of future studies concerning labour analgesia. One could speculate whether a reduction in pain score to 0–1 on a scale of 0–10 when the parturient would be happy with a pain score of 5–8 represents overreaction or overdose. In clinical practice, the large variation in pain scores which are acceptable, suggests that instead of using a general cut-off point one should use an individual one. This is one way for the mother to have active input, which is important for a satisfactory birth experience as noted by Hodnett (2002).

In a paper attempting to quantify the PID with clinical significance, Farrar *et al.* (2001) suggested that the patient request for rescue medication is the product of the patient weighing the properties (side and analgesic effects) of the rescue drug. In order to investigate this further, the parturients in study III were asked to give a reason for not increasing the PCA dose if the current pain score was higher than the individually set acceptable pain score. The fact that approximately one third of the parturients did not achieve the acceptable pain score during remifentanil analgesia giving a reason related to side effects demonstrates how remifentanil does not always provide enough analgesia. That some of the parturients do not dare to take a larger dose for fear of increasing side effects supports the suggestion by Farrar *et al.* (2001). When the mother decides whether to increase the PCA bolus during dose escalation she probably balances the possibility of increasing the side effects (by increasing the dose) with sustaining the pain (by not increasing the dose). Most probably a similar decision is also made when deciding whether to press the PCA trigger when a fixed dose is used. In fact, some women learned to press the trigger at every 2nd or 3rd contraction in the studies with fixed PCA dose which was most probably one of the reasons why the idea of perfect timing of the PCA bolus did not work in reality, in study IV. In this group of parturients, the suggestion by Olofsson *et al.* (1996b) is probably still valid that it is not possible to increase the systemic opioid dose enough to result in a significant analgesia because of the extensive sedation precluding further dose escalation.

In studies II and IV, a special definition was used for reference value for PID calculation in order to compensate for the increase in pain as labour progresses which would have caused a period effect in the analyses of the cross-over study. This definition, however, is subject to an inherent bias due to a possible hyperalgesia caused by remifentanil which Koppert *et al.* (2003) noted even after a short remifentanil infusion in volunteers with experimental pain. As a result, there may be an overestimation in PID in these two studies and study I which also employed the same method of calculating the PID. The *post hoc* analysis done for the sake of this dissertation, however, is free from this possible bias.

The reduction of pain scores by a median of 3.5 compared with the baseline pain calculated for the time the 34 parturients were using their individual effective doses probably represents the maximum analgesia which can be attained with remifentanil IVPCA. It should be noted, however, that 13 out of 47 parturients did not reach the individual effective doses in studies I and III for various reasons. Remifentanil analgesia also failed to produce the expected result in a significant

proportion of parturients using other methods of measuring success. Nineteen percent of women would not have liked to continue with remifentanil and 14% parturients reported a mean pain relief score of less than 2 (corresponding to no or slight pain relief) during analgesia. These findings are consistent with the fact that in most other studies concerning remifentanil in labour there has been a proportion of parturients who needed regional analgesia due to inadequate pain relief (table 3).

It is interesting that there was no difference between EDA and remifentanil IVPCA in several variables related to patient satisfaction in study III, such as pain relief score, proportion of parturients not reaching the effective dose and proportion of parturients willing to continue with the given medication in spite of the fact that pain scores were lower with epidural. This may be a new observation due to the fact that the current study was blinded while earlier RCTs comparing systemic opioids with epidural (table 2) were not. Another possible explanation is that remifentanil IVPCA provides better labour pain relief than traditional opioids. However, an ultra-dilute epidural solution was employed in this study to be able to keep the parturient unaware of which medication she was randomised to receive. Most probably, an epidural solution containing more of the local anaesthetic would have further reduced pain intensity and possibly there would have also been a difference in the variables related to patient satisfaction.

In study IV, there was a period effect with higher pain scores, lower PID and lower pain relief scores although there was larger drug consumption during the second study period. There are two possible explanations for this finding. Firstly, pain tends to increase as labour progresses. Secondly, there is an acute opioid-induced hyperalgesia through enhancement of the N-methyl-D-aspartic acid (NMDA) receptor response which has been noted in rat dorsal horn cell cultures after as little as 36 minutes exposure to clinically relevant concentrations of remifentanil (Zhao and Joo 2008). Volunteer studies suggest that a similarly rapid post-infusion hyperalgesia exists in humans as well, while development of an acute tolerance was not observed during a 3 hour infusion with clinically relevant doses (Koppert *et al.* 2003, Angst *et al.* 2009). The current investigation is unable to clarify the degree to which these two possible mechanisms – pain increase as labour progresses and development of acute hyperalgesia – would affect the results. There was a difference in the PID between the two study periods, however, even though the PID calculation method was designed to compensate for the increase in pain as labour progresses. This argument supports the explanation that an acute, opioid-induced hyperalgesia plays a larger role in the period effect

observed in a cross-over trial than does the physiological progress of labour. Indeed, in other clinical settings, an increased need for analgesics has been observed after remifentanil based anaesthesia for surgery (Guignard *et al.* 2000, Ahonen *et al.* 2000).

When parturients are allowed to use nitrous oxide together with remifentanil, 50–90% of them actually use it (Volikas & Male 2001, Thurlow *et al.* 2002, Blair *et al.* 2005). This could be a reasonable action if the observation of study IV concerning acute hyperalgesia is valid and the mechanism behind it is based on an acute tolerance through enhancement of NMDA receptor response (Zhao and Joo 2008). Nitrous oxide could function not only as an additive analgesic but also as a NMDA antagonist preventing hyperalgesia (Jevtović-Todorović *et al.* 1998, Richebé *et al.* 2005). This, however, is highly speculative and should be tested experimentally in human volunteers as well as in clinical studies.

Nitrous oxide provided little analgesia in study II. The lag between the moment of beginning to breath N_2O and the maximal pain during the uterine contraction was probably too short to allow an effective concentration to be built up into the alveoli and subsequently at the site of effect. This is supported by the fact that the highest exhaled N_2O concentration during the PCA boluses was only 30%. This was somewhat lower than the maximum ETN_2O of 36.5% reported by Einarsson *et al.* (1996). It is possible that coaching the parturient to anticipate the forthcoming uterine contraction would have resulted in a better analgesia, but it is felt that the manner in which nitrous oxide was used in our study reflects the routine practice on many labour wards.

6.2 Dosing of remifentanil in labour analgesia

The median remifentanil consumption during the study period (studies I-III) and the two study periods (study IV) of 0.07 μg/kg/min is comparable with the doses recommended by the manufacturer for postoperative analgesia and conscious sedation when a continuous infusion is employed. It is also comparable with the consumption of remifentanil when IVPCA is employed for analgesia and sedation during painful procedures such as colonoscopy (Ackaboy *et al.* 2006, Fanti *et al.* 2009). In comparison with papers reporting consumption of remifentanil during labour analgesia, the parturients in the current study used remifentanil in the lowest range (Volikas *et al.* 2005, Balcioglu *et al.* 2007, D'Onofrio *et al.* 2009), most probably reflecting the fact that remifentanil was only used for a short time in the current study, whereas the other studies employed remifentanil for the

entire duration of labour. There are several mechanisms which could increase analgesic consumption towards the end of labour, including an increase in pain intensity as a result of the physiological progress of labour and the development of acute hyperalgesia. The latter possibility is suggested by the larger consumption observed during the second study period in study IV, during which time higher pain scores were also noted.

Parturients in studies I and III were allowed to titrate the PCA bolus until they answered ”no” to the question whether they would like to have more efficient analgesia. The median effective PCA bolus of 0.4 μg/kg and consumption of 0.085μg/kg/min are comparable with the doses used in routine clinical practice with spontaneously breathing parturients. The upper range of the dose and consumption is far beyond this. In particular, parturients in the transitional phase seemed to reach an effective analgesia with a larger consumption of remifentanil compared with parturients in the earlier phases of labour. The doses and consumption found efficient by a proportion of parturients were larger than those that have previously been reported as life-threatening remifentanil analgesia during labour in which a continuous infusion of 0.1 μg/kg/min was given (Waring *et al.* 2007). This suggests that there is no safe effective dose to be applied in general, but that the effective dose should be determined individually. There was a larger consumption at the effective dose in study III than in the open study. This probably largely explains the differences observed in the side effects between the study designs.

There were 5 out of 24 parturients in study III who found the preset maximum dose of 0.9 μg/kg ineffective. These and some other parturients of the 13 not able to find an effective dose in studies I and III in the post hoc cohort might have achieved it if the maximal dose in the protocol had been higher or the time available for dose escalation longer. This suggests that even higher PCA boluses than those allowed in the current investigation could be used in selected cases.

The systematic review by Arnal *et al.* (2009) presents a scheme for a titration of remifentanil dose with 0.2 μg/kg as the starting point. The correlation between the baseline pain and the effective dose suggests that a larger starting bolus would probably better suit parturients with a very high pain score before commencement of analgesia. There were four out of 47 parturients, however, whose individual effective dose was 0.2 μg/kg (figure 5) even with a high baseline pain score, which finding supports the starting dose suggested by Arnal *et al.* (2009).

The main finding of study IV was that the timing of the remifentanil bolus during the uterine contraction cycle has no importance when a 1 minute PCA-bolus is employed. The larger PID in the subgroup with a long and stable contraction interval (after correction for the excess number of bad demands in the periods with a delayed bolus) suggests, however, that there may be a patient population which might benefit from an optimised drug delivery regimen. The power analysis of the study also suggests the possibility for a type 2 error with a difference of 2 steps in the pain score 0–10 as clinically significant. If the second study period is disregarded as suggested by Altman (1991), the results include a difference of 1 step in pain scores between the two different dosing regimens with no statistical significance with this sample size. These results might have been different with a larger sample.

6.3 Side effects

6.3.1 Respiratory effects

There are two different theories concerning the mechanisms which possibly cause desaturation during labour. Minnich *et al.* (1990) suggested that desaturations during labour are the result of irregular breathing patterns in painful labour. Porter *et al.* (1992) concluded that opioids cause desaturation as a side effect during labour analgesia.

In the present study, Porter's conclusions were supported by the fact that there was a larger consumption of remifentanil among the women needing oxygen supplementation during the entire study period in studies I, III and IV and during the effective dose in studies I and III, as well as larger effective PCA boli. The current investigation is unable to exclude the mechanism suggested by Minnich *et al.* (1990), however, as this was supported by the observation that pain scores were higher during analgesia among those requiring oxygen supplementation. Higher pain correlated with a higher consumption of remifentanil and this, again, supports the conclusion by Porter *et al.* (1992).

Women requiring oxygen supplementation were larger in weight and BMI but the difference was small. The association was also fairly weak although it was statistically significant. Its clinical significance may be in the fact that one should be cautious in applying remifentanil IVPCA in obese parturients. There are two possible reasons for this association. Firstly, doses based on actual weight may

lead to relatively larger effects in overweight subjects as suggested by the pharmacokinetic study by Egan *et al.* (1998). Secondly, the smaller functional residual capacity of the lungs caused by obesity makes the labouring woman susceptible to more rapid desaturation during the contraction pauses when the ventilation of the lungs is weaker. The maximum weight and BMI in the current study were 109 kg and 39.9 kg^2/m, respectively. The doses noted in the current investigation should only be applied in a more obese population with extreme caution.

In clinical practice, as Arnal *et al.* (2009) concluded, the clear difference in the incidence of hypoxaemia in study III confirms that supplemental oxygen should be used during remifentanil analgesia in labour in order to prevent desaturation. In a minority of cases, however, hypoxaemia may be refractory to oxygen supplementation as was apparent in two cases in study III and 5 cases out of 612 parturients reported by Hodgkinson & Hughes (2008). The clinical significance of these observations of desaturation refractory to oxygen supplementation is that SaO_2 monitoring is mandatory even if oxygen supplementation is begun prophylactically. Another apparent conclusion is that pain does not prevent hypoxaemia as oxygen supplementation was needed more frequently among women with larger pain during analgesia (table 10). The proportion of parturients with desaturation might have been higher if the current investigation included longer study periods or were extended to cover the entire duration of labour.

Oxygen saturation was lower with remifentanil than during nitrous oxide inhalation, even though PID was lower during the latter. This finding could be explained by the fact that the parturients spent more time inhaling 50% oxygen along with nitrous oxide during the nitrous oxide periods. This result is in accordance with the other cross-over studies in which nitrous oxide did not result in hypoxaemia (Carstoniu *et al*. 1994, Yeo *et al*. 2007). It also supports the suggestion by Irestedt that when there is no concomitant use of opioids, intermittently inhaled nitrous oxide in oxygen does not negatively influence maternal oxygenation between contractions (Irestedt 1994).

The fact that respiratory rate was similar during and before analgesia and that $ETCO_2$ was only slightly elevated in comparison with nitrous oxide suggests that the source of hypoxaemia during labour analgesia with remifentanil is shallow breathing i.e. low tidal volume during the contraction pauses instead of bradypnoea and hypoventilation. The $ETCO_2$ of 3.7 measured during contractions with nitrous oxide is comparable with the $ETCO_2$ reported by Einarsson *et al.*

(1996) suggesting pain induced hypocapnia. This was partially corrected by remifentanil analgesia. The gas sampling method includes a possibility of marked dilution but the similarity with the results in the study by Einarsson *et al.* (1996) suggest this did not substantially alter the findings in the present study. This result should be confirmed in future studies with blood gas analysis.

The respiratory rates observed during study I were lower than the mean rate of 17.6 noted in the study by Volikas *et al.* (2005) during remifentanil analgesia. Our low values were probably due to problems in the monitoring method being unable to sense breaths with low tidal volumes. In fact, the observed problems in impedance monitoring led us to abandon this variable during the later studies. The fact that there was no difference in respiratory rate before and during analgesia is in accordance with Mitsis *et al.* (2009) who noted that low TCI had little effect on the respiratory rate.

The larger consumption of remifentanil was probably the reason why women with oxygen supplementation provided higher sedation scores. The timing of the remifentanil bolus did not make a difference in the proportion of parturients requiring oxygen supplementation or the mean SaO_2 during analgesia.

6.3.2 Sedation and dizziness

With regards sedation, the current study suggests that remifentanil analgesia is safe as all women remained conscious and were able to respond verbally to the questions – in spite of relatively high subjective sedation scores. The number of parturients in the current study is, however, too small to prove safety in this respect. Indeed, there have been two cases of unconsciousness mentioned in the literature, one of which was life threatening (Balki *et al.* 2007, Waring *et al.* 2007). In routine clinical use, in the environment of the delivery rooms without the constant vigilance of anaesthesia personnel, deep sedation, unconsciousness and apnoea could easily lead to death or injury. In the current investigation, remifentanil seemed to be associated with stronger sedation than epidural analgesia and nitrous oxide. It is quite possible that - especially if there is a dosing error – unconsciousness with apnoea would follow administration of remifentanil to a labouring woman.

The procedures of preparation of the syringe, entering the dose in the PCA device and preparing the IV-line with anti-reflux valve are subject to human error. During the clinical studies required for the initial registration of remifentanil, several cases of respiratory depression and apnoea occurred when remifentanil

was infused inadvertently, e.g., with flushing of the intravenous line during administration of another drug or from residual remifentanil left in the tubing after discontinuation. For these reasons *inter alia*, the FDA approval was granted on condition that the label indicate that remifentanil can only be used in highly monitored settings (operating room or postoperative recovery room) under the supervision of an anaesthesia practitioner (Landow *et al.* 1999). A normal delivery room is usually not such a place.

To date - including all the parturients in the systematic study by Arnal *et al.* (2009), the recent reports by Evron *et al.* (2008), D'Onofrio *et al.* (2009), Tveit *et al.* (2009), the three quality control studies reported as conference abstracts (Hodkinson and Hughes 2008, Harbers *et al.* 2008, Foley and Hill 2009), the cases not included in the analyses in studies I - III and the parturients in study IV - the global experience regarding the safety of remifentanil in obstetric analgesia is based on experience of analgesia in 2969 parturients. If no repeated reporting of same cases has taken place within this population, only 1 case with a life threatening situation has occurred, with no mortality or permanent disability. A simple calculation of the upper limit of 95% confidence interval (3/n) for occurrence of accident resulting in death or handicap gives 1/1000 with the current experience (Eypasch *et al.* 1995). It must be noted, however, that a major proportion of the cases have been reported in abstracts based on audit or regional database data which may not include all the necessary data for exclusion of near miss situations or even major accidents. Until large clinical studies and quality control reports are presented including thousands of parturients with remifentanil analgesia, remifentanil in obstetric analgesia should be regarded as experimental requiring strict supervision by the anaesthetists, one-on-one nursing and a routine monitoring of alertness and SaO_2.

In study IV, there was a trend toward less sedation when the PCA bolus was optimised to give its peak effect during the uterine contraction. This observation is in accordance with the paper by Balki *et al. (*2007) in which less sedation was noted when the background infusion was increased instead of the PCA bolus. This could be a starting point for developing a better drug delivery system. The fact that the varied drug delivery resulted in better pain relief in neither of these two studies suggests that different parts in the central nervous system – those responsible for analgesia and those producing sedation after μ-receptor action – may have a different temporal pattern in their activation. Indeed, Leppä *et al.* (2006) noted differences in the times to peak activity in different brain areas in fMRI after a fast bolus of remifentanil.

The fact that approximately one third of parturients, who did not reach an acceptable pain score during remifentanil analgesia, gave a reason related to side effects for not increasing the dose, provides us an indication as to why remifentanil does not always provide enough analgesia. Some of the parturients do not dare take a larger dose as they fear an increase in side effects. Possibly, better systemic analgesia with remifentanil could be achievd by using adjunct medication with synergistic analgesic properties but different side effects, especially if the adjunct medication could prevent the development of acute hyperalgesia as suggested in chapter 6.1. Nitrous oxide, ketamine or clonidine could be employed (Koppert *et al.* 2003, Richebé *et al.* 2005). This again is, however, highly speculative and would need further experimental and clinical research not only due to of the uncertainty of whether the observations in rodents and human volunteers could be translated to labour analgesia, but also because of the potential risks associated with combination treatments.

Dizziness was one of the two side effects that parturients in study III stated were an obstacle in titrating the dose up to an effective level. Unfortunately, the protocol of the current study did not include recording it, but 24 out of 114 parturients spontaneously reported dizziness during the study periods. Many others used variable expressions such as the feeling of being drunk.

6.3.3 Nausea, vomiting and other maternal side effects

Although opioid analgesia has a reputation as a medication which causes nausea and vomiting, remifentanil was not strongly linked with nausea in the current studies. One out of four parturients reported nausea at baseline before the induction of analgesia. This was carried over into the study period in approximately half of them, albeit at a milder level. After remifentanil had been started, another subgroup of women appeared with opioid-induced nausea, but still the proportion of parturients with nausea was not higher during remifentanil analgesia than before analgesia. The clinical relevance of these findings is that the presence of nausea before remifentanil analgesia is planned is not a reason to recommend another form of analgesia as there is a good change that it will become milder or even disappear.

The current study suggests links between the classical risk factors of PONV and nausea during remifentanil labour analgesia. Both previous PONV and a history of motion sickness were associated with nausea during remifentanil analgesia. However, they were not associated with an increase in nausea scores

(most often from 0 i.e. no nausea before the study) when remifentanil was started. This limits their usefulness in clinical practice. A relative lack of analgesic effect of remifentanil was associated with both the incidence of nausea and an increase in nausea during remifentanil analgesia, which supports observations made on postoperative pain that pain has at least a partial role in the mechanisms behind nausea during labour (Andersen *et al.* 1976).

Only in study IV was there a comparable observation time before the initiation of remifentanil IVPCA. This study suggested an increase in vomiting during the medication compared with baseline. This finding is not surprising as it is known that opioid analgesia interferes with emptying of the stomach (Nimmo *et al.* 1975). During the current studies, eating was not forbidden, but there is no record of what was actually ingested. In order to decrease the risk of pulmonary aspiration in case of a general anaesthetic, it is probably advisable to discourage feeding during IVPCA remifentanil. In this respect, one should keep in mind that parenteral opioid analgesia was an exclusion factor in the large study by O'Sullivan *et al.* (2009) which did not find evidence of harm of food intake during labour.

Itching was observed in only approximately one out of four of the parturients in the first original studies (I and II). This result is at variance with the finding by Olufolabi *et al.* (2000) of all four parturients expressing facial pruritus and one of them having severe generalised pruritus causing her to withdraw from the study. As pruritus was weak in most of the cases and did not appear as a problem the item was omitted from the two last studies.

There were no haemodynamic problems associated with use of remifentanil, nitrous oxide or EDA in the current population. The haemodynamic stability during remifentanil analgesia was in line with findings by Blair *et al.* (2001), Blair *et al.* (2005), Evron *et al.* (2005), Balki *et al.* (2007), Balcioglu *et al.* (2007) and D'Onofrio *et al.* (2008). A decrease > 15% of systolic pressure and heart rate was observed by Volikas *et al.* (2005) in 3 and 5 cases, respectively, during the first hour of analgesia in a cohort of 50 parturients receiving remifentanil. These threshold values were, however, much higher than the definitions for hypotension or bradycardia in the current investigation or in the other papers with information concerning haemodynamics during remifentanil labour analgesia.

6.3.4 Effects of remifentanil analgesia on the foetus and the neonate

The interpretation of FHR varies according to the criteria used by the obstetrician. This was probably the reason why the proportions of tracings interpreted as pathological varied so much between the original studies although the same obstetrician analysed all the tracings in this investigation. A large proportion of the FHR tracings were classified as abnormal or pathological during remifentanil analgesia. In most of these cases, there was a normal tracing immediately before analgesia or shortly after cessation of it suggesting a causal association. In comparison with nitrous oxide and EDA there was no difference in the proportion of abnormal FHR tracings but a type 2 error is possible in small samples in the original studies II and IV as FHR tracing abnormality was not included in the power analyses when the studies were designed.

The UV:MA concentration of remifentanil is high, 0.73–0.88, and the foetus is subject to the effects of remifentanil soon after the mother receives IV remifentanil. The mechanism by which remifentanil results in FHR changes is probably the same as with other opioids i.e. a direct foetal μ-receptor agonist action by the placentally transfered remifentanil. The intensity of remifentanil effect on foetal CNS may be more intense, however, due to the higher placental transfer than what has been noted with sufentanil, alfentanil or fentanyl (Helbo-Hansen 1995). This potent foetal remifentanil action has been successfully used for foetal immobilisation during fetoscopic surgery (Van de Velde *et al.* 2005). Assuming that the results of Doppler ultrasound measurements with sufentanil are applicable to remifentanil, the opioid induced FHR changes are not an indication of foetal distress (Alahuhta *et al.* 1993). Moreover, sedation and analgesia have been demonstrated to alleviate hypoxaemia via a mechanism of decreasing vascular resistance and increasing maternal cardiac output when the mother is under stressful stimulation (Morishima *et al.* 1979). Normalising the hypocapnia caused by painful labour has the potential to improve foetal oxygenation through an enhanced release of oxygen from maternal haemoglobin (Motoyama *et al.* 1967).

In 14 out of 22 cases with abnormal FHR in studies I-III, the deviations included reduced variability, missing macrovariability or early decelerations which could be classified as benign (National Collaborating Centre for Women's and Children's Health 2007). In most cases with abnormalities which are often interpreted as more ominous (sinusoidal, variable decelerations, late decelerations, reduced microvariablility combined with late decelerations), the findings did not

result in an obstetric intervention during the study or during the follow-up period. From the perspective of the small proportion of emergency caesarean sections in other studies summarised in table 4, it seems the two cases of FHR tracing abnormalities leading to obstetric interventions (one grade I emergency CS and one foetal capillary blood sample) in the current investigation may represent random events. There were at least two cases with foetal capillary blood samples taken after the study period, however, which suggest that if the remifentanil exposure had been longer this might have resulted in an increased rate of foetal blood gas sampling.

In a review article concerning paediatric anaesthesia, Marsh and Hodkinson (2009) made reference to case reports of severe bradycardia in neonates and children during the use of remifentanil in intensive care and as a part of general anaesthesia (Briassoulis *et al.* 2007, Weale *et al.* 2004, Wee *et al.* 1999). They also listed 6 studies in which no significant bradycardia was observed with remifentanil. However, these papers did not include neonates and only one study included infants - all of whom were > 2 moths of age (Crawford *et al.* 2005). Future studies should address the potential of remifentanil for causing FHR pathology and whether, for example, foetal ST-wave analysis could differentiate benign opioid-induced FHR tracing abnormalities from true pathological findings.

In clinical practice, the opioid induced benign FHR abnormalities associated with remifentanil labour analgesia are a problem for obstetricians. Reduced beat-to-beat variability may obscure other significant changes in the FHR. Alarming FHR tracing may prompt foetal scalp capillary blood sampling or even unnecessary obstetric interventions.

The fact that there was no association between the need for oxygen supplementation and the FHR abnormalities should not be understood in such a way that there is no need for oxygen supplementation. This finding may have been due to close monitoring and treatment which was possible in the conditions of a clinical trial but which may not be possible in a routine clinical application of the analgesic method. It may be advisable to prevent maternal hypoxaemia with supplemental oxygen. The importance of maintaining good oxygenation was revealed when Huch *et al.* (1977) showed an improvement in foetal transcutaneous oxygen tension when the mother was given supplemental oxygen.

Babies born within 30 minutes of the cessation of remifentanil showed no depression in comparison with the babies with a longer last dose to delivery interval. In this finding, the current investigation is in accordance with the other studies concerning the status of the newborn indicating good Apgar scores after

remifentanil analgesia, even when the analgesia has been extended up to the second stage of labour (table 3). Van de Velde *et al.* (2004) noted a significant proportion of neonates suffering from respiratory depression warranting mask ventilation when remifentanil was used as a part of the medication in the general anaesthesia for caesarean section. Although the dose used in anaesthesia (0.5 μg/kg followed by infusion at 0.2 μg/kg/min) was larger than the ones used with labour analgesia on average, the dose escalation method leads to comparable individual doses with remifentanil IVPCA as indicated by the higher end of the consumption range in the current study (0.32 μg/kg/min). This may therefore have a profound effect on the neonate in case of a very short delay from the last maternal dose to delivery. A strong exposure to opioids could also blunt the foetal sympathoadrenal activation associated with vaginal delivery which has been suggested as an important factor in respiratory adaptation in the neonate (Irestedt *et al.* 1984).

6.4 Methodological considerations

Clinical research concerning pregnant women requires specific ethical consideration. Any depressant action of medicines given to the parturient may have deleterious effects on the mother, foetus or the newborn. This is true, in particular, with opioids which have the capacity for causing respiratory depression and apnoea.

Remifentanil appears to have an advantage over the other opioids used routinely in labour analgesia such as pethidine, fentanyl or sufentanil. The elimination of the drug is fast and nondependent on liver function, even in the neonates (Ross *et al.* 2001). Even with this advantage, however, remifentanil could result in respiratory depression, which could require immediate intervention such as an antidote (naloxone) or supporting oxygenation and ventilation. Moreover, it is not known whether there is a tendency with remifentanil to accumululate on the foetal side of the placental barrier in cases with foetal acidosis. For these reasons, the studies were designed to include only a brief exposure over a maximum of 1 hour (studies I-III) or over a limited number of uterine contractions (study IV). The studies were also timed to include only the first stage of labour in order make sure that there was enough time for the foetus to redistribute and metabolise remifentanil before delivery. There was an anaesthetist or a nurse anaesthetist present in the labour room throughout the study periods and immediately after them. The equipment included both the

antidote and tools needed in ventilatory support of both the mother and the newborn.

An effort was made to reach the parturients as early as possible during labour when a possibility of participating in the study existed, to inform the parturients as to the advantages and possible side effects of the drugs used in the trials. After a preliminary screening by the midwives, the parturients were interviewed personally by the research personnel. It was explained that participation or declining would not have any influence in the way the parturients were treated in the institution. The parturients were given written information and a written consent was required.

The recruitment procedure had an inherent bias of possibly selecting an extraordinary group of parturients (courageous, open minded, pain tolerant etc.) instead of representing a balanced sample of the population of parturients as a whole. The proportion of consenting parturients is unknown as there are no records of whom the midwives have asked to join the study and whom they preferred not to ask. Given the difficulty of conducting research in the labour ward, however, these shortcomings have been thought to be inevitable. Moreover, it was assumed that the possible selection bias was similar for both of the groups in the only parallel study and during both study periods during the two cross-over studies. In terms of parity and age, the distribution in the current study (table 7) seems to follow the national statistics (National Institute for Health and Welfare (2008)) according to which the proportion of primiparae has been approximately 42% during the last decade while it was 36% in the post hoc cohort. The average parturient in Finland is 30 years old while she was 28 in the current cohort.

The current investigation was designed to cover only a small part of the first stage of labour. This fact makes it difficult to apply the current results in clinical practice where remifentanil analgesia is used through the entire painful part of the labour. This may be a problem specifically concerning the respiratory effects of remifentanil. Parturients in the transitional phase seemed to reach an effective analgesia with a higher consumption of remifentanil compared with parturients in the earlier phases of labour and the parturients needing oxygen supplementation reached the effective dose at a higher level than those who did not need oxygen supplementation. These observations suggest that the proportion of parturients with desaturations could have been even higher if the current investigation included longer study periods or were extended to cover the whole duration of labour. The frequently observed FHR changes might also have prompted more foetal capillary blood sampling if the remifentanil analgesia had been longer.

The *post hoc* cohort analysis includes cases from the four studies with many similarities in study design which supports the validity of this analysis. The subjective variables included in the post hoc analysis included questions given to the parturient similarly in all 4 studies, with the exception of nausea, which included a different subjective scale in study II. This discrepancy was resolved by analysing the presence of nausea dichotomously and by considering only an increase or decrease in the score during analgesia compared with the baseline score and the scores given after the study period. The inclusion of cases rejected from the analyses in the original studies improves the external validity of the current investigation making the results more applicable to the clinical work where it is not possible to know whether the labour will progress faster than anticipated. The cases with protocol violations also represent situations encountered in clinical reality where nitrous oxide is given together with opioids or remifentanil is given intentionally or unintentionally in larger doses than what was established as a median effective dose in study I.

In the *post hoc* cohort analysis, it is impossible to control possible biases caused by differences in the protocols of the studies such as the length of exposure or the cervical dilatation or inclusion of parturients from another institution (study III). The criteria for commencement of oxygen supplementation were slightly different in study I compared with studies III and IV but in practice it was felt that the threshold for oxygen supplementation was actually quite similar as the pattern of appearance of desaturations was periodic and in most cases in studies III and IV, repetitive desaturations took place before the nasal cannula had been attached and supplemental oxygen begun. Nevertheless, the results of the *post hoc* cohort analysis should be applied with caution, especially with regards variables with which researcher interpretation is included.

Cohort analyses include no randomisation and are subject to biases which are thought to be less probable in RCTs. This is why the findings based on the original studies including a design of a RCT should be seen as core evidence in the current investigation. The observations in the *post hoc* analysis should be interpreted with caution as merely providing a framework for the temporal pattern of the effects of remifentanil IVPCA, as well as possible associations between parturient characteristics, doses and effects of the analgesia to suggest hypotheses for future studies.

Blinding of the parturient was successful in studies II-IV. The researcher present in the delivery suite was able to distinguish the medication in each patient by the end of the study period in most of the cases (table 11). Even in the cases

where the researcher knew the medication, however, the blinding unfolded little by little during the study period either by the analgesic effect or by the conspicuous side effect of sedation.

Table 13. Blinding quality control in the original studies.

Study	Parturient was able to say the study medication		Researcher guessed correctly
	Correctly	Incorrectly or did not want to guess	
Study II n=15	4	11	15
Study III n=45	18	27	41
Study IV n=41	15	26	33
total n=101	37	64	79

7 Conclusions

1. There is a wide variation in the individual effective doses required to achieve effective pain relief, and it is difficult to find a single dose suitable for all parturients.
2. Remifentanil IVPCA provides better analgesia than intermittently inhaled 50% nitrous oxide. Remifentanil IVPCA produces more sedation than nitrous oxide analgesia.
3. EDA gives better analgesia than IVPCA with remifentanil when the aim is to lower the pain scores. In terms of pain relief score - and the proportion of parturients willing to continue the given medication - remifentanil analgesia worked as well as EDA with dilute local anaesthetics during the 60 minute trial. Compared with EDA, remifentanil IVPCA is associated with more sedation and desaturation.
4. Giving an IVPCA remifentanil bolus during the uterine contraction pause does not improve the pain relief for the majority of parturients.
5. The fact that remifentanil IVPCA was used during the labour of 114 parturients without serious complications adds to the global experience of remifentanil as a labour analgesic. The safety of remifentanil, however, is yet to be confirmed. Remifentanil has an inherent potential for life-threatening complications. The continuous monitoring of SaO_2 and sedation level and adequate safety measures (including availability of the antidote and close supervision by professionals experienced in using remifentanil) are therefore mandatory.

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I Volmanen P, Akural EI, Raudaskoski T & Alahuhta S (2002) Remifentanil in obstetric analgesia: a dose-finding study. Anesth Analg 94: 913–917.

II Volmanen P, Akural EI, Raudaskoski T, Ohtonen P & Alahuhta S (2005) Comparison of remifentanil and nitrous oxide in labour analgesia. Acta Anaesthesiol Scand 49: 453–458.

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