Remifentanil as analgesia for labour pain

by

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Contents

1. Acknowledgements

The study was performed at Women's Department (labour unit) and Department of Anaesthesia and Intensive Care at Sørlandet Hospital HF, Kristiansand during the period 2004 to 2008. The work has been based on a collaboration between Sørlandet Hospital HF and Department of Surgical Sciences, University of Bergen.

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2. Abstract

Aims

To collect updated information about pharmacological labour analgesia in Norway, especially systemic opioids and epidural. Evaluation of efficacy and safety with remifentanil IVPCA (intravenous patient-controlled analgesia) for pain relief during labour. To compare remifentanil IVPCAwith epidural analgesia (EDA) regarding efficacy and safety during labour.

Methods

In paper I, two national surveys identified Norwegian labour analgesia methods and changes during the study period (2005-2008). Paper II is a prospective, observational study of analgesic efficacy and safety with remifentanil IVPCA. Paper III is a prospective, randomized controlled trial comparing remifentanil IVPCA with EDA regarding analgesic efficacy and safety.

Results

The surveys in paper I found the frequency of EDA in Norwegian hospitals to be increasing, but still low (25.9%) compared to other western countries. Nitrous oxide and traditional systemic opioids, like pethidine, were frequently used. In paper II remifentanil IVPCA was found to give satisfactory labour analgesia in more than 90% of the parturients with an average maximal pain reduction of 60%. Maternal oxygen desaturation and sedation were acceptable, and neonatal data reassuring. In paper III, a randomized controlled trial found remifentanil IVPCA and EDA to be comparable both regarding analgesic efficacy (pain reduction) and maternal satisfaction. Remifentanil IVPCA produced more maternal sedation and oxygen desaturation, neonatal outcome was reassuring in both groups.

Conclusions

The frequency of epidural labour analgesia in Norway has increased, but is still relatively low. Nitrous oxide and traditional systemic opioids are frequently used. The clinical practice seems conservative, newer short-acting opioids are seldom used for systemic labour analgesia. The studies on remifentanil IVPCA revealed adequate pain relief, high maternal satisfaction, and no serious neonatal side effects. There were no differences in analgesic efficacy, maternal

satisfaction, and neonatal outcome when comparing remifentanil IVPCA with EDA. However, remifentanil caused maternal sedation and oxygen desaturation. We recommend the use of IVPCA remifentanil as labour analgesia instead of traditional opioids as pethidine and morphine when EDA is not an option. The presence of skilled personnel and close monitoring is mandatory.

3. List of papers

I. Tveit TO, Halvorsen A, Rosland JH.

Analgesia for labour: a survey of Norwegian practice – with focus on parenteral opioids.

Acta Anaesthiol Scand 2009; 53: 794-799.

II. Tveit TO, Halvorsen A, Seiler S, Rosland JH.

Efficacy and side effects of intravenous remifentanil patient-controlled analgesia used in a stepwise approach for labour: an observational study.

Int. J Obstet Anesth (accepted 2012)

III. Tveit TO, Seiler S, Halvorsen A, Rosland JH.

Labour analgesia: a randomized, controlled trial comparing intravenous remifentanil and epidural with ropivacain and fentanyl.

Eur J Anaesthesiol. 2012 Mar;29(3):129-36.

4. Abbreviations

IV=intravenous

IM = intramuscular

IVPCA=intravenous patient-controlled analagesia

IVNCA=intravenous nurse-administrated analgesia

EDA=epidural analgesia

PCEA=patient-controlled epidural analgesia

CSE=combined spinal-epidural analgesia

MA=mothers artery

UA=umbilical artery

UV=umbilical vein

N_2O=nitrous oxide

LA=local anesthetic

PDPH=post dural puncture headache

CSD-time=context-sensitive decrement time

FHR=fetal heart rate

CTG=cardiotocography

STAN=ST-segment analysis

5. Background

5.1 Introduction

Labour is known to be a very painful processs,[1-3] so the ability to offer adequate pain relief is therefore important. Most women request some kind of pain alleviation during labour and delivery.[4, 5] Epidural analgesia is regarded as the "gold standard" for obstetric analgesia,[3-9] but this regional technique may be unsuitable or not always possible to perform. In addition, many women prefer other analgesic methods for various reasons.[10] Effective and safe alternative analgesic methods should therefore be available for parturients.[5, 9, 11, 12]
Nitrous oxide and parenteral opioids have long traditions as labour analgesics.[9, 13-17] Pethidine has been the most frequently used opioid for decades worldwide.[5] In a survey by Barrat-Due and colleagues from 2005, they found that 11.7% of parturients in Norwegian labour units received systemic opioids, and pethidine was the most frequently used drug (80%).[13] Another survey from the UK published in 2007, focusing availability of other methods than regional blocks, demonstrated that 95.5% of the responding units used intramuscular pethidine or diamorphine. Intravenous patient-controlled analgesia (IVPCA) was offered by nearly half of the responding units (49%); remifentanil was most commonly used (34.6%), followed by morphine (29.5%) and fentanyl (26.9%).[15] Lavand'Homme and Roelants concluded similarly in a recent survey from Belgium; almost half of the responding labour units (47%) used intravenous patient-controlled analgesia when EDA was not an option, and remifentanil reported to be the first choice (76.5%, this included both living births and intrauterine deaths).[9]
There has been a continuous debate as to whether the main effect of pethidine is sedative or analgesic, and the practice regarding pethidine seems more based on traditions than scientific evidence.[13, 14, 18] Morphine has been recommended and used as an alternative.[19] However, both pethidine and morphine have active metabolites that may induce side effects in the newborn due to residual systemic analgesia.[13, 20]
The use of epidural analgesia (EDA) for labour pain has increased significantly during the last two decades, both internationally and in Norway.[7, 9, 13, 21] In the same period, newer opioids with rapid onset, short half-life and no active metabolites have been introduced for labour analgesia. These provide new opportunities to optimize individual pain treatment for

parturients, with less cumulative effect in mother, fetus and newborn. [22-25] It has therefore been suggested that newer opioids, like fentanyl and remifentanil, should replace pethidine and morphine as parenteral labour analgesics.[9, 12, 19, 26, 27] Chassard et al surveyed the use of intravenous opioids during childbirth in French maternity units, and found sufentanil (70%) to be preferred for IVPCA.[28] Data from other European surveys also demonstrate use of short acting opiods, as discussed above. North-American labour institutions seem to have traditions for use of fentanyl as systemic labour analgesic.[21]

Absence of 24-hours epidural service is common worldwide, and in developing countries neuraxial analgesia may not be an option. In a global perspective, safe and low-cost analgesia methods should be available for obstetric pain relief. Alternative methods to epidural therefore need to be explored, and research on this topic is important, aiming for effective and safe analgesia methods for both the mother and her baby.[5]

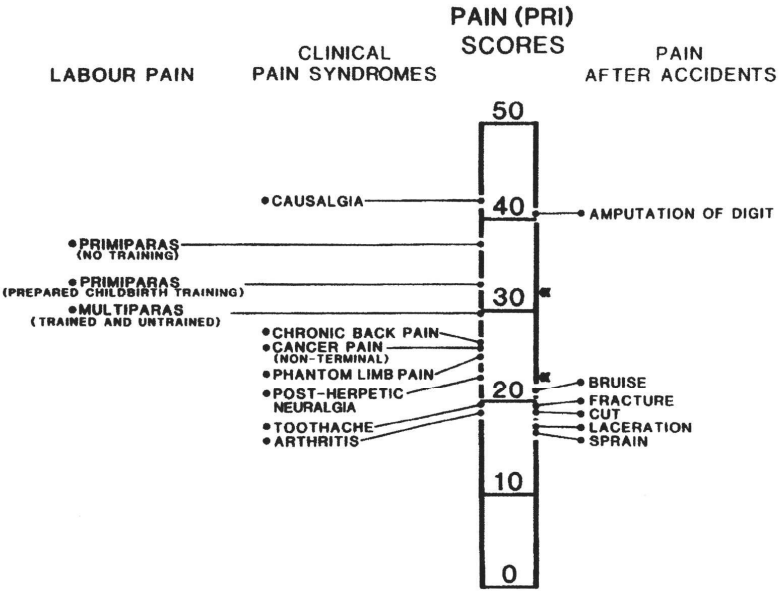

Fig 1. Comparison of pain during labour compared to different clinical pain syndromes and after accidents (from Melzack 1993, with kind permission from the publisher).[2]

5.2 Labour pain

Childbirth is regarded as one of the most painful experiences during womens life [2] (Fig.1), and this sensation of acute pain is known to be a complex process.[5, 11, 29-32] Acute labour pain is known as a dynamic process with intermittent uterine contractions. It is characterized by increasing pain as labour progresses, which normally resolves immediately after delivery.[5, 32] The neurophysiological mechanisms for labour pain includes Aδ and C nerve fibre activation conducting nociceptive impulses from the body of the uterus to the spinal cord, mainly at level of the 11th and 12th thoracic dorsal roots, with some overlap into10th thoracic and first lumbar roots. These fibers accompany sympathetic nerve fibers in this area. During the first part of labour parturients feel pain from lower abdomen and the lumbar region. During second stage the pain is conducted via nerve fibers from the vagina and perineum (S2-S4); the pudendal nerve, the ilioinguinal nerve, the genitofemoral nerve and the long cutaneous nerve of the thigh. After entering the dorsal horns, the nociceptive impulses are conducted via interneurons and travel through the spinothalamic tract to the brain[32-36] (Fig 2).
In addition, the subjective experience of labour pain is influenced by multiple physiological and psychosocial factors. The response to sensory stimuli from the labour process, both during uterine contractions and cervical dilatation, is therefore extremely multidimensional.[5] It is also evident that among parturients, the experience of pain is very individual with large differences in pain scores. This underlines the need for recognition of individual needs, and to adjust pain relief according to this.[2, 30]

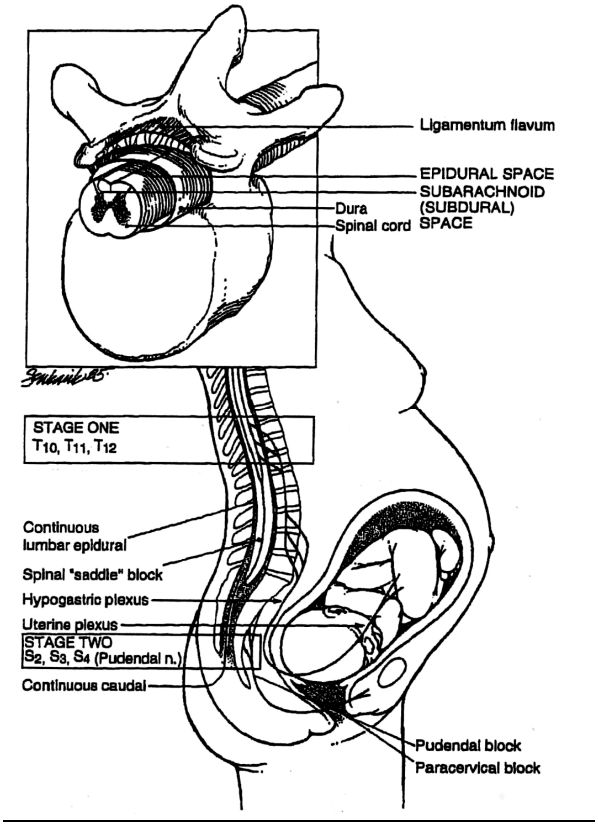

Fig 2. Spinal and epidural anatomy for regional obstetric analgesia (from Althaus 2005, with the kind permission of the publisher).[21]

5.3 Labour analgesia

Non-pharmacological methods and techniques

With normal procedure, parturients are initially offered non-pharmacological analgesic methods as warm packages, warm bath (hydrotherapy), subcutanous injection of sterile water, acupuncture and transcutaneous electrical nerve stimulation (TENS). Aromatherapy, antenatal preparation and support during labour (one-to-one) are other techniques anticipated to relieve pain.[35]

Pharmacological methods

When labour progresses through the active phase of first stage (Fig 3), pharmacological methods are often offered to relieve the increasing pain, either as analgesics given systemically, or as an neuraxial blockade.[30, 37, 38] EDA is effective and safe, and known as "the gold standard" method.[13, 18, 39-42] The frequency of epidural- or spinal/CSE analgesia during childbirth has increased during the last two decades, both in Norway and other western countries.[9, 18, 41, 43, 44] According to Gaiser, in USA the use of epidural labour analgesia was doubled from 1981 to 1992 (larger hospitals up to 51%), and the frequency is still increasing.[44] Other authors describing North American practice have concluded similarly.[21] In European countries, the average frequency of EDA during labour is varying; from around 20% and up to nearly 70%.[9] Barrat-Due and colleagues stated that also in Norway the epidural frequency was doubled from 1996 to 2002 (10.7% vs 20.6%), and the highest frequency reported in 2002 was 40.5%.[13]

In addition to EDA, nitrous oxide and systemic opioids have long traditions used for obstetric analgesia. For instance, pethidine has been widely used for decades, and is a well known drug with low cost, and easy to administrate. However, traditional systemic opioids, such as pethidine and morphine, represent challenges regarding the parturient, because labour pain resolves immediately after delivery with risk for overdosing and opioid side effects after birth. These opioids are also characterized by long plasma half-life and active metabolites. Nearly all systemic opioids cross the placenta,[45, 46] and can therefore also give side effects in the fetus and newborn.[5, 34, 47]

Use of newer, short-acting opioids without active metabolites give possibilities for improved analgesic efficacy, and less neonatal side effects. Both fentanyl, alfentanil, sufentanil and remifentanil have been used.[9, 15, 28] Commonly used pharmacological methods for obstetric analgesia are given in Table 1.

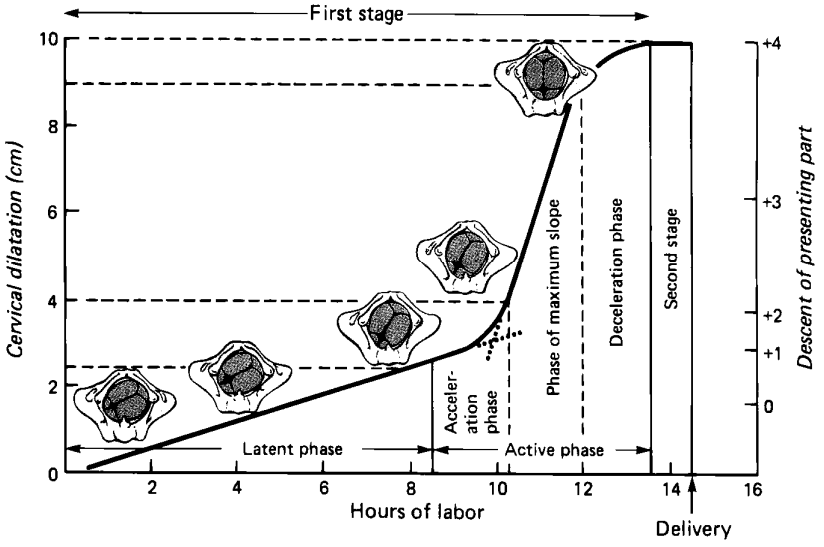

Fig 3. The course of normal labour (from Morgan Jr GE, Mikhail MS (editors): Clinical Anesthesiology, second edition. Appleton & Lange, 1996. With kind permission from the publisher).[34]

Table 1. Pharmacological methods for pain relief during labour and delivery.[7, 17, 48, 49]

Method/technique	Efficacy	Side effects	Comment
Regional analgesia			
EDA	Very good	Hemodynamic	Anesthesiologist needed
Spinal	Very good, rapid onset	Hemodynamic, pruritus	As EDA, short duration
CSE	As EDA/ spinal	As spinal	As EDA
Systemic analgesia			
Pethidine	Poor analgesia, but slightly better than placebo	Sedation, nausea	Drug and metabolites accumulate in fetus
Morphine	Poor/modest	As pethidine	Metabolites
Fentanyl	Superior to pethidine	Less nausea and sedation than pethidine	Respiratory depression and desaturation
Alfentanil	Rapid onset	Similar to fentanyl	Hypotonia
Sufentanil	Slow onset	Neonatal desaturation	Deposition of drug in placenta
Remifentanil	Good, rapid onset	Desaturation, sedation, nausea	
Inhalation analgesia			
Nitrous oxide	Moderate	No apparant	Low cost, polluter

EDA=epidural analgesia

CSE=combined spinal-epidural analgesia

5.4 Regional analgesia

Epidural analgesia is today the preferred method for alleviation of pain during childbirth, and is demonstrated to be both effective and safe.[4, 47, 50] Spinal analgesia has been used as an alternative regional technique to a minor, but slightly increasing degree. A combination of these techniques, combined spinal-epidural (CSE) analgesia, is also used; with a single shot spinal anesthesia producing a rapid onset of pain relief, followed by an epidural catether infusion with the possibility to extend analgesia if needed.[7, 21, 49] There are two main indications for regional labour analgesia; labour pain, or pregnancy complicated by disease or increased risk during labour and delivery.[33]

Epidural analgesia

The most effective method for control of labour pain is epidural,[6, 8, 43, 47] this method is therefore regarded as "the gold standard". However, this is an invasive procedure requiring an anaesthesiologist. Medical contraindications, including bleeding disorders,[6, 51, 52] may hinder the use of an epidural. Alternatively, EDA may be unwanted by the parturient or technical impossible to perform.[15, 21, 44, 53] In Norway the labour services are organized in three levels (level 1-3). Smaller units are served by midwifes only, and cannot offer epidural analgesia for their parturients (level 3). Some labour units have anaesthesiologist available, but not as 24-hours service (level 2). Therefore, many women in labour cannot be given EDA even though indicated.[43]

Normally EDA analgesia is started with a bolus dose of a dilute solution of a local anesthetic and an opioid, and maintained by continuous infusion.[34, 54, 55] This epidural solution can be administrated as regular top-ups (bolus by midwife), continuous infusion, conventional patient-controlled epidural analgesia (PCEA),[8, 56-59] or computer integrated PCEA.[35, 60-64] The use of PCEA and computer integrated bolus doses have by some authors been advocated to optimize analgesia and prevent breakthrough pain resulting in a reduced consumption of local anesthetics.[64]

With administration of low-dose local anesthetics, as bupivacaine and ropivacaine,[65, 66] in combination with an opioid as sufentanil or fentanyl,[8] it is evident that EDA does not increase the frequency of Caesarean section,[4, 41] but may induce longer labours, increased need for

oxytocin stimulation, and increased frequency of instrumental delivery.[4, 40-42, 49, 67-70] Traditionally, EDA reduced the parturients mobility during childbirth. With epidural solutions containing low-dose local anesthetics combined with opioids, this problem is reduced ('mobile epidural').[4, 64]

Potential maternal side effects include hemodynamic instability and pruritus, as well as nausea/vomiting, urinary retention, respiratory depression,[3, 4, 58, 71-74] and impaired breast feeding.[4, 47, 52, 70, 75-77] Epidural associated fever is still discussed, but so far without evidence.[3, 4, 52, 78, 79] Regarding neonatal outcome the overall effect of EDA is positive.[50, 70, 80] Complications to epidural may occur; accidental perforation of dura with post dural puncture headache being the most frequent. More serious complications as intraspinal or intravenous injection of epidural drugs, neurological injury and sequeles, epidural hematoma and epidural infection have been reported, although rare.[4, 6, 39, 40, 51, 53, 81-85] Back pain is a common symptom after childbirth, but in a study by Loughnan and a review from the Cochrane Collaboration, they found no significant differences between EDA and systemic opioid analgesia.[4, 86] Recommendations for safe clinical practice should be followed, and adequate clinical observation is important to detect early symptoms, and take immediate action when needed.[6, 50]

Spinal analgesia

The last years spinal analgesia has also been used for pain relief during vaginal labour and delivery. With single-shot spinal analgesia, containing a long-acting local anesthetic and/or an opioid agonist, one can achieve effective analgesia with a rapid onset.[49, 52] Of course, this method is limited by the fact that duration cannot be extended.[7, 35] But when requesting analgesia late in labour, the spinal technique could be considered as an option, especially for multiparous.[52, 57, 87, 88] Known maternal side effects are pruritus,[64, 89] nausea/vomiting, and respiratory depression. Respiratory arrest has been reported with repeated doses of sufentanil.[90] The risk for post dural puncture headache should always be considered. Non-reassuring FHR-changes as bradycardia has also been discussed.[3, 49, 74, 87, 91-94] Thus, the increased risk of FHR abnormalities must be considered before using subarachnoidal injection of opioids.[64]

Combined spinal-epidural analgesia (CSE)

CSE is today a commonly used method for labour analgesia in many countries.[3, 8, 49, 64, 95] This method offers rapid onset of spinal analgesia by low dose of a local anesthetic or an opioid, or a combination of these drugs.[52] The epidural catheter inserted makes it possible to extend analgesia, maintenance of EDA is normally achived by a solution of low-dose local anesthetic and an opioid agonist.[3, 7, 48, 49, 60, 64, 87] Efficacy and potential side effects are the same as for spinal and epidural analgesia separately.[87, 91, 92, 94] Theoretically, this combination of the two neuraxial methods should be an advantage: fast onset, reliable and high-quality analgesia, and high maternal satisfaction.[64] But several previous studies have concluded that overall CSE- and epidural analgesia are comparable regarding efficacy, safety and maternal satisfaction.[49, 87, 92, 96] Increased costs due to equipment needs and close follow up must also be weighed against potential positive effects by use of CSE.[91, 92]

Other nerve blocks

By use of a local anesthetic, both paracervical block and blockade of the pudendal nerve can be utilized as supplement to alleviate pain during labour and delivery.[11, 31, 32, 50] When indicated, these nerve blocks are normally performed by obstetricians and midwives.

5.5 Systemic labour analgesia: Nitrous oxide and parenteral opioids

In certain clinical situations regional analgesia may not be an option; it may be unavailable, contraindicated, imposible to perform, or not wanted by the parturient.[5] For these women, an effective and safe analgesia alternative should be available.[97]

Nitrous oxide

Nitrous oxide is the only inhalational analgesia that has reached widespread use for alleviation of labour pain,[14, 31, 70] although more potent agents have also been used.[14, 17, 31, 98]
Nitrous oxide has been used in labour since the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934.[98, 99]
The mechanism of action of nitrous oxide is thought to be an increased release of endorphin, dopamine, and other natural pain relievers in the brain, which modulate pain stimuli via descending spinal cord nerve pathways. Nitrous oxide does not completely relieve the pain of labour but creates "diminished pain, or a continued awareness of pain without feeling bothered by it". Nitrous oxide also has an antianxiety effect, which may be helpful if laboring women are restless and doubt their ability to cope.[98]
Normally, it is given as a 50:50 mixture of oxygen and nitrous oxide. N_2O has a rapid onset and termination of action,[14, 17, 47, 98, 100] the efficacy depends on adequate N_2O blood concentration at the peak of painful uterine contractions. This could be achieved by starting the inhalation as soon as the parturient first feels contraction pain, and stop inhalation after the peak of pain.[11, 35] Of course, this technique also includes positive aspects of patient-controlled therapy; the patient contributes by self-administration, and by this given the possibility to control some of the factors alleviating pain.[14, 34] N_2O is easy to administer, have relative low costs, with tolerable side effects, and is safe for parturients and and their babies.[14, 17, 70, 98, 100-102]

Nevertheless, nitrous oxide emissions may be a risk to personnel in the working area. In a global perspective, it is regarded as an atmospheric polluter, and the use should therefore be restricted.[70]

Parenteral opioids

Use of systemic opioids has a long tradition in labour analgesia, especially pethidine has been widely used.[5, 14, 26, 97] However, side effects and lack of evidence for analgesic efficacy have been the main criticism.[5, 14, 26, 103-105]

Other opioids with a theoretically more suitable pharmacological profile have been used as alternative [9, 15, 22] (Table 2). Of these, remifentanil seems to be the most promising.[70, 106]

Of course, the parturient needs close monitoring because increased risk of side effects with such a potent opioid; skilled personnel and monitoring equipment are needed. All systemic administered opioids cross the placenta, with risk for neonatal respiratory depression, this side effect can be reversed by use of naloxone if needed.[46]

Both subcutanous, intramuscular and intravenous administration have been used for different opioids.[14] Using the intravenous route, opioids can be given by midwife on demand, or as patient-controlled analgesia (self-administration). Women in labour receiving systemic opioid analgesia demonstrate great variation in respons to doses administered. This individual response to opioid therapy is a well known fact that could only partly be explained by genetic variants.[1, 107, 108] Pain relief during childbirth can also be achieved by a combination of systemic opioids and nitrous oxide.[33]

As a general warning; for all pharmacological labour analgesia and anesthesia, one should be aware of the potential risk for pulmonary aspiration of gastric content, and "nil per os" policies are still discussed.[101]

Pethidine

Pethidine is the most frequently used systemic opioid during the past decades [5, 11, 70] because it is recognized to be; a well-known analgesic, given by midwives, easy to administer, and associated with a low cost.[5, 16, 17, 104] It was introduced into obstetric analgesia in the 1940s, and soon replaced morphine mainly because early studies demonstrated lower risk of respiratory depression compared to morphine.[26] But pethidine has been demonstrated to have limited analgesic efficacy,[20, 26, 103, 109, 110] and maternal side effects like sedation, respiratory depression and nausea is common.[14, 17, 33, 70, 103, 104] It crosses the placenta, and active metabolites (norpethidine) have been found in the newborn up to 72 hours after delivery, risking serious neonatal side-effects like sedation, neurological dysfunction, respiration

depression, and delayed initiation of breastfeeding.[5, 14, 17, 26, 33, 35, 80, 104, 111] Pethidine is known to have a narrow therapeutical window, and the use of pethidine in labour has been extensively discussed and criticised; giving more sedation than analgesia.[5, 103, 104]

Morphine

Morphine has been used in obstetric analgesia since the late 1800s, but its efficacy and safety regarding both mother and child are still discussed. Some studies have concluded with better pain relief by use of morphine compared to pethidine, and that morphine should be prefered for obstetric use.[19, 26] Other authors have questioned the analgesic efficacy of morphine used for pain relief during labour.[17, 26, 103, 112] Morphine has slow onset, compared to more lipid-soluble compounds, but is quickly metabolized, mainly by glucuronidation, and eliminated from maternal circulation.[14, 26] The main metabolite, morphine-3-glucuronide, has no analgesic activity,[17, 35, 113] but has been shown to have neuroexitatory effects with high concentrations.[113] Within doses used for obstetric analgesia, morphine has possibly less negative effects on the neonate compared to pethidine and its metabolites.[14] However, one should be aware of morphine-6-glucuronide, which is an active and potent metabolite of morphine with longer half life.[113, 114]

Fentanyl

Fentanyl is a synthetic, highly lipid soluble and protein bound opioid, with greater potency than morphine and pethidine, with rapid onset of action (3-4 min to peak effect) and short duration.[14] It has no active metabolites, crosses the placenta, but has less maternal and neonatal side effects than pethidine.[26, 115, 116] Previous studies have found fentanyl superior to pethidin and alfentanil regarding analgesic efficacay during labour,[22, 38] and can be used as an alternative to EDA.[38, 116] Used for second trimester genetic termination of pregnancy, fentanyl had satisfactory analgesic efficacy and less side effects than morphine.[117] Fentanyl can be administered intravenous by midwife (IVNCA) or as IVPCA.[17, 23] It should be noticed that maximum dose is limited, as repeated doses increase the context-sensitive decrement time (the time to a 50 % reduction in blood concentration after cessation of a steady infusion).[80] With high doses, one should be aware of possible neonatal depression.[17, 80, 95, 116, 118-120]

Since 2005 Sørlandet Hospital in Kristiansand has used intravenous fentanyl (midwife administered/IVNCA) as parenteral labour analgesic (local guidelines). Based on available evidence, the parenteral labour analgesia procedure was changed from IV pethidine to IV fentanyl.[5, 104] The labour department/unit has about 2000 deliveries per year.

Alfentanil

Alfentanil is a synthetic lipofilic opioid, with higher protein binding than other opioids. It is characterized by rapid onset of action (1 min) and short duration, and with higher potency than morphine and pethidine. The CSD-time is shorter than for fentanyl.[80] Compared to fentanyl, the analgesic efficacy during labour is also less,[17, 22] and alfentanil seems to produce more neonatal neurobehavioural depression than pethidine. The use of alfentanil for systemic pain relief during labour is limited.[80]

Sufentanil

Sufentanil is characterized by high lipophilicity and potency, and short context-sensitive decrement time. The time to peak effect is slow though (4-6 min), and relatively low potency. The drug has been associated with risk for placental deposition and neonatal respiratory depression. Sufentanil is not commonly used for systemic labour analgesia, but has gained great popularity and is widely used for intrathecal and epidural analgesia.[80]

Remifentanil

Remifentanil is a potent, selective μ-opioid receptor agonist, normally around 70% protein bound. This synthetic opioid is characterized by a rapid onset of maximal peak effect (1.2-1.4 minutes), and is rapidly hydrolysed by non-specific blood and tissue esterases (ester linkage) of unlimited capacity. This gives a constant context-sensitive half-life, with a short elimination half-life of approximately 3-10 minutes, and a predictable short duration and rapid offset of action. The elimination is independent of dose, duration of infusion and organ function (liver, kidneys). The metabolites have insignificant activity (1/300-1/4600 the potency of remifentanil).

Theoretically, this should be the ideal opioid for systemic labour analgesia, but the optimal dose and administration method is still investigated. Remifentanil was first registered for general anaesthesia 1996.[38, 80, 121]

Kan and colleagues studied serum analyses from mothers artery (MA), umbilical artery (UA) and umbilical vein (UV) after Caesarean section, performed in epidural anaesthesia and with concomitant remifentanil infusion until skin closure. They demonstrated that UV:MA and UA:UV ratio for remifentanil was 0.88±0.78 and 0.29±0.07, with a mean clearance of 93 $ml \cdot kg^{-1} \cdot min^{-1}$.[122] This indicates that remifentanil crosses placenta and is rapidly metabolised and distributed in the child. However, even if the drug may give maternal sedation and respiratory depression, there was not reported any serious incidents for mother or child. Nevertheless, such potential side effects require one-on-one nursing and adequate maternal and neonatal monitoring.[80]

Already in the late 1990s remifentanil was used for general anaesthesia and postoperative analgesia to both infants and small children. The studies reported satisfactory results regarding efficacy and safety.[123-127] Experience and evidence from intensive care medicine demonstrate no accumulative effects of remifentanil used for sedation and analgesia. The drug seems to be safely administered to patients with reduced function of vital organs, even long time infusions are well tolerated without accumulative effects.[114, 128]

Remifentanil labour analgesia; Clinical studies

Early series of case reports were based on use of remifentanil for labour because of contraindications to epidural; coagulation disorders, renal impairment and cardiac disease. In these case reports, remifentanil was evaluated to be useful, with no complications to parturient or newborn.[129-131]

Further reports on small number of patients also concluded that remifentanil could be helpful to alleviate pain during normal labour.[132, 133] Olufolabi and colleagues included four parturients in a preliminary study of remifentanil IVPCA, giving 0.25-0.5 $\mu g \cdot kg^{-1}$ with a lock-out time of five minutes. The anaesthesiologist bedside was allowed to give extra doses on-demand. The study was interrupted because of unsatisfying analgesia and maternal opioid related side effects. There were no neonatal side effects reported.[134]

Later remifentanil studies have shown promising analgesic efficacy using patient controlled intravenous administration.[24, 135-141] Only two studies have compared remifentanil with epidural analgesia.[142, 143]

But all these studies have limitations precluding a consistent conclusion; either few participants, too short observative duration, infrequent observations, or inappropriate registration of efficacy or side effects.[24, 137, 144, 145] Different administration methods and dosing regimens have been proposed, but so far the optimal mode of administration and appropriate doses have not been found.[24, 27, 135-138, 142, 144]

It has earlier been stated that remifentanil readily crosses the placenta.[24, 122, 146] Maternal and neonatal safety issues are still discussed, especially sedation and ventilatory depression, but so far without conclusive evidence. The need for more studies and larger study populations have been emphasized.[12, 27, 144]

A recent observational study by D'Onofrio was promising for remifentanil given as continous IV infusion, but the results from pain registrations included only a short initial phase.[147] In another recently published randomized study by Douma and colleagues, comparing remifentanil with meperidine and fentanyl, remifentanil produced better analgesic efficacy, but the pain scores in all three groups returned towards baseline (pre-treatment values) late in labour.[38] Remifentanil IVPCA has also been used as an alternative to EDA during labour of twins.[148] In addition, with short duration and rapid offset of action, remifentanil makes it possible for the parturient to have full mobility throughout the course of labour.

Other systemic analgesics

Other systemic analgesics as meptazinol, nalbuphine, butorphanol, pentazocine, tramadol, piritramid and ketamine have also been used for pain relief during childbirth. These analgesics seem to be used to a limited exent so far.[5, 9, 17, 31, 80, 149]

Table 2. Main characteristics of systemic opioids commonly used for labour analgesia.[17, 38, 80]

	Pro	Con	Comment
Pethidine	-Familiarity -Low cost	-Modest analgesia -Active metabolites -Neonatal side effects (3-5 days)	-Long traditions used for labour analgesia -More sedative than analgesic
Morphine	-Rapidly cleared from mothers circulation	-Modest analgesic effect	-Limited evidence used for labour analgesia
Fentanyl	-Analgesic efficacay better than pethidine -Rapid onset -Various administration methods (IV, IM, SC, DERM, PO)	-CSD time increased -Potential neonatal respiratory depression (dose-dependent)	-Widely used for neuraxial labour analgesia
Alfentanil	-Rapid onset of action -Short duration	-More neonatal depressant than pethidine -Analgesic efficacy less than pethidine	-Limited use for parenteral labour analgesia -Highly proteinbound
Sufentanil	-CSD time short	-Slow onset -Possible placental deposition -Potential neonatal respiratory depression	-Limited use for parenteral labour analgesia -Commonly used for neuraxial labour analgesia
Remifentanil	-Rapid onset -Rapid degradation -Inactive metabolites -Constant CSD time -Analgesic efficacy better than pethidine and fentanyl	-Maternal sedation -Maternal desaturation -Administration by iv.pump only	-No accumulation -Rapidly metabolized in the neonate -Organ independent elimination (tissue and blood esterase)

CSD-time=context-sensitive decrement time.

IV=intravenous, IM=intramuscular, SC=subcutaneous, DERM=transdermal, PO=peroral.

5.6. Maternal satisfaction

Maternal satisfaction related to childbirth is a complex concept, and influenced by many factors during the labour process.[3, 5, 58] This multidimensional issue is therefore challenging to evaluate and measure, both in research and daily clinical practice.[58] Previous studies have used many different methods and approaches for measurement, making it difficult to compare the results.[150] The degree of pain relief is the main subject for most parturients, although other factors could influence satisfaction too; thus personal expectations, amount of support from caregivers, the quality of the caregiver-patient relationship, and involment in decision making have been demonstrated as key factors for maternal satisfaction.[5]
Pain relief and satisfaction are therefore not equated, but two different dimensions to be focused when evaluating labour analgesia.[31, 151] For example; epidural is known as the most effective method for labour analgesia, but a recent review from the Cochrane Collaboration demonstrated no significant difference in maternal satisfaction when comparing EDA to parenteral opioids.[4] It is assumed though that both analgesic efficacy and side effects of analgesia will be of some importance for the parturients experience and satisfaction ratings. Nevertheless, inclusion of patient's satisfaction in evaluation of obstetric analgesia has been emphasized.[150]

5.7. Norwegian labour services

At the time we performed our studies, the Norwegian labour services were defined in three levels[152]: Level 1 (district general- and university hospitals): More than 1500 deliveries per year, obstetrician on call, anaesthesiologist on call, paediatrician on call, newborn intensive care department. Level 2 (local hospitals): More than 400–500 deliveries per year, obstetrician on call, anaesthesiologist on call, paediatrician associated (not on call).
Level 3 (midwife-led delivery unit, 'fødestue'): More than 40 deliveries per year, only midwife on call (no caesarean section/vacuum/forceps deliveries, no epidural service).
About 75% of all deliveries take place in level 1 service, 24% in level 2 and only 1% in level 3.

6. Aims of the study

The main aim was to explore current practice and propose new and better pain relief in labour.

Our main hypothesis were: 1. Norwegian systemic labour analgesia seemes to be more based on traditions than evidence. 2. Newer short-acting opioids as remifentanil could possibly replace tratiditional opioids for IV labour analgesia. 3. There seems to be a need for improved and individualized pharmacological pain therapy to those parturients who cannot be given EDA.
Theoretically, remifentanil have a suitable pharmacological profile for obstetric analgesia. A well-known opioid used for surgical anaesthesia, postoperative analgesia and intensive care (analgesia and sedation)[114] may also be used in a new clinical setting; pain relief during childbirth. A main intention with our clinical studies was a transfer of existing evidence, clinical skills and experience from anaesthesiologists to obstetricians and midwives. By this, our main hypothesis could be tested, and with an opportunity to improve systemic opioid labour analgesia.[26]

The overall aims with the present thesis were:

1) To identify changes and collect updated information about pharmacological labour analgesia in Norway, especially the use of systemic opioids and epidural (paper I).
2) To evaluate the efficacy and safety of remifentanil IVPCA for pain relief during labour, including metabolism of remifentanil in the neonate (paper II).
3) To compare remifentanil IVPCA with epidural analgesia regarding efficacy and safety during labour (paper III).

7. Methodological considerations

Data from all Norwegian labour wards were collected in 2005 and 2008 in paper I. In paper II and III, the the participants were included consecutively for these prospective studies. The study behind paper II was an observational study, while paper III was based on a randomized controlled trial. All the participants signed a written informed consent before inclusion, and were allowed to withdraw any time during the study period.

7.1. National survey of methods and drugs used for pharmacological labour analgesia, with monitoring of changes during a 4-years periode (paper I)

In Norwegian hospitals, pethidine has been commonly used for decades as the preferred opioid for systemic labour analgesia. This practice seemed more based on traditions than evidence. The analgesic efficacy has been questioned, while side effects as sedation are well known. Morphine has been recommended and used as an alternative. In addition, N_2O has been widely used to alleviate labour pain, either as the main therapy, or as supplement to other analgesics. But nitrous oxide is a known polluter, therefore environmental concerns have restricted the use of this inhalational analgesic. During the past two decades the frequency of epidural labour analgesia has increased in Norway, as in most areas of the Western world. The epidural frequency in our hospital, however, has stayed low compared to other hospitals of similar size. Based on available evidence, Sørlandet Hospital in Kristiansand changed the procedure for systemic labour analgesia in 2005; replacing IV pethidine with IV fentanyl. With this background we wanted to explore the Norewegian pharmacological labour analgesia services, and collect updated information to monitor development during the research period. We had special focus on the use of systemic opioids and EDA frequency.

A questionnaire concerning obstetric analgesia was sent to all labour units in Norway 2005, in 2008 we repeated the questionnaire to all institutions with more than 1000 childbirths per year (85% of all births). The questionnaire requested statistical birth reports and clinical policy concerning labour analgesia, and focused on pharmacological methods for pain relief during labour. We requested information only on living births: Number of deliveries,

pharmacological methods, EDA frequency, local anaesthetics and opioids for EDA, use of nitrous oxide, systemtic opioids, and routes and methods for systemic opioid administration. The questionnaire contained free text boxes to fill in relevant information, and the repeated questionnaire in 2008 contained some additional questions to seek more detailed information.

7.2. Prospective observational study of remifentanil IVPCA used for labour analgesia (paper II)

Parturients of ASA status I or II, primi- or multipareous, normal term singleton pregnancies, with regular uterine contractions, cervical dilatation larger than 2-3 cm, expected vaginal delivery, normal fetus in cephalic presentation, pregnancy without known complications, normal cardiotocographic, and normal gestation age (37-40 weeks) were included. The exclusion criteria were contraindications to remifentanil, pethidine given < 8 hours before start of remifentanil analgesia, or request for epidural analgesia.

They received remifentanil as a stepwise IVPCA bolus dose regimen with no background infusion. Starting dose was 0.15 $\mu g \cdot kg^{-1}$ with increasing or decreasing dosing steps of 0.15 $\mu g \cdot kg^{-1}$. Dosing was allowed to be adjusted every 15.minute, depending on individual response. No maximum dose was defined. Dose adjustments depended on VAS pain score, parturient's request, registered side effects and clinical observations by the investigator. The calculation of pca doses was based on estimated body weight by the following formula: patient body height minus 100 = estimated weight (kg). Remifentanil hydrochloride (Ultiva®, GlaxoSmithKline) was diluted in saline to a concentration of 50 $\mu g \cdot ml^{-1}$. The lockout period was two minutes.

Remifentanil IVPCA was administered using a pca pump (Baxter 6060 Multi-Therapy infusion pump, Baxter Healthcare Corporation, Kista, Sweden) with a bolus infusion speed of 2 $ml \cdot min^{-1}$ (100 ug min^{-1}). The parturients were allowed to use the pump until delivery. The observer registered consumption of remifentanil manually, in addition to automatic registration in the pca pump.
Blood samples were collected from the umbilical cord for serum concentrations of remifentanil and its metabolites (artery, vein).

7.3. Prosepective, randomized controlled clinical trial comparing remifentanil IVPCA with routine epidural analgesia (paper III)

Women of physical status ASA I or II and of mixed parity were included if: normal pregnancy and gestagion age (37-40 weeks), single and normal sized fetus, no suspected fetal pathology, regular uterine contractions, cervical dilatation > 2 cm and normal cardiotocographic pattern. Exclusion criteria were request for epidural analgesia, use of pethidine within 8 hours before start, or any information of contraindications to remifentanil. The participants were randomized to two groups; the RA group receiving intravenous patient-controlled analgesia with remifentanil, or the EA group using epidural analgesia with ropivacain and fentanyl according to the department's routine method. The randomization was based on a computer generated list according to numbers, with codes kept in sealed envelopes until study start.

The RA group received remifentanil hydrochloride (Ultiva®, GlaxoSmithKline) diluted in saline to a concentration of 50 μg ·ml^{-1}. This solution was given as stepwise bolus doses with no background infusion. Starting dose was 0.15 μg·kg^{-1}, and with increasing dose steps of 0.15 μg·kg^{-1} and no maximum limit. The dose was allowed to be increased or decreased every 15.minute according to the parturients request for dose adjustment, VAS pain score and side effects. The lockout period was 2 minutes. The bolus infusion speed of remifentanil was 2 ml·min^{-1} (100 μg·min^{-1}). Remifentanil IVPCA was administrated using a pca pump (Baxter 6060 Multi-Therapy infusion pump, Baxter Healthcare Corporation, Kista, Sweden). Calculation of pca doses was based on estimated bodyweight by the following formula; patients body height minus 100 = estimated weight (kg). The remifentanil consumption was registered automatically in the pca pump and manually by the observer.

Parturients randomized to EDA had an epidural catether inserted in midline at level L2-3/L3-4 by the investigator. They received a continous epidural infusion of ropivacain 1 mg·ml^{-1} and fentanyl 2 μg·ml^{-1} ("walking epidural"). An initial bolus dose of 10 ml, followed by a 5 ml top-up after 5 min (total 15 ml), was given before start of infusion (start dose: 10 ml·hour^{-1}). Midwife was thereafter allowed to adjust the infusion dose (5-15 ml·hour^{-1}), and give rescue doses of 5 ml if needed. If inadequate analgesia, the anaesthesiologist controlled the epidural catheter and adjusted the position, or a new EDA-catheter was placed if necessary.

7.4. Maternal monitoring and registrations (paper II and III)

The parturients were closely observed and monitored by anaesthesiologist, midwife and obstetrician. The investigator (senior anaesthesiologist) stayed in the delivery department during the study period, and the parturients were continuously observed by the attending midwife.

Maternal heart rate (HR) and oxygen saturation (SaO_2) were monitored continuously throughout the study period. Respiratory frequency (RR), non-invasive systolic bloodpressure (SBP), diastolic bloodpressure (DBP) were registered every 15.minutes. All physiological parameters were recorded by use of a separate monitor (Nonin 2120, Scan Med AS, Drammen, Norway).

Observer sedation score was registered before start (baseline), and every 15.minute by investigator and attending midwife without comparison, using a five-point verbal rating scale: 1=alert, 2=slightly drowsy, 3=drowsy, 4=very drowsy, 5=unrousable.

Pain score collected by the anaesthesiologist was recorded before start of analgesia, and every 15.minute. The parturient was not allowed to compare with her previous scores.

Pain assessment was registered on a horizontal visual analogue scale (VAS) (0-100 mm; 0=no pain, 100=worst imaginable pain). Registrations were performed before start of analgesia (baseline), and every 15.minute for the first two hours. The VAS score was based on experienced pain the last 15 minutes period, and the parturient was not allowed to compare with her previous pain scores. After two hours, the VAS score was performed every 30.minute if the patient was clinical stable. After adjustment of the dose, pain score was registered after 15 and 30 minutes. Before baseline registration, the patient should have experienced 1-2 vaginal contractions without analgesia, and thus having the best possible foundation to evaluate the analgesic efficacy. The VAS pain registrations were performed as long as the patient received pain relief, and data were collected by the investigating anesthesiologist. Midwifes clinical impression of the parturients level of pain were also monitored by the same method (VAS). Midwife and patient were not allowed to see each others VAS pain scores.

Observations of nausea, vomiting and itching were also registered.

Analgesia was stopped at time of delivery. Parturients who delivered within 30 minutes were not included in data analysis. If conversion from remifentanil to epidural, data collected until conversion were included in analysis.

All participants were asked to fill in a questionnaire regarding satisfaction with analgesia and side effects (five-point categorical scale) within 24 hours after delivery. In addition, the attending midwife evaluated impressions of analgesia and side effects by the same method (questionnaire, five-point categorical scale). Mother and midwife were not allowed to see each others evaluations.

7.5. Maternal side effects and practical handling (paper II and III)

For parturients receiving remifentanil IVPCA, supplemental oxygen (4 liters·min^{-1}) was administered via nasal cannula if SaO_2<92%. [136, 139] Remifentanil analgesia would be temporarly stopped if persistens of SaO_2 < 92%, RR < 9 breaths·min^{-1}, SBP < 90 mmHg or HR < 50 beats·min^{-1}. When physiological parameters were normalized, pain therapy could be started again on a one step lower dose.
The EA group was handled in accordance with the departments clinical routines. Oxytocine, metoclopramide, ephedrine and intravenous fluids were available if needed. Equipment and drugs for handling of hemodynamic and respiratory problems were immediate available (Basic Life Support).

7.6. Fetal/neonatal monitoring and registrations (paper II and III)

Fetal heart rate (FHR) was continuously monitored. A combined fetal heart monitor (Stan S21, Neoventa Medical, Götenborg, Sweden) was used for external monitoring (cardiotocography, CTG) and invasive fetal monitoring (ST-analysis, STAN) as warranted for obstetrical indications. The FHR-tracings were analyzed by an obstetrician according to the department's clinical guidelines, and remifentanil was stopped if pathological changes occurred; absence of accelerations, decreased variability, bradycardia, tachycardia, or late decelerations.

After the study, FHR registrations were evaluated separately by two obstetricians blinded to analgesia method and neonatal outcome.

Apgar scores 1, 5, and 10 minutes after delivery were recorded, and umbilical blood gas analysis was performed according to standard procedures (arterial and venous pH, CO_2, O_2, BE).[46] Routine paediatric examination of the neonates was undertaken within 48 hours after birth, pathology or complications were recorded.[70] Neonatal need for naloxone and resuscitation were registered.[46, 47, 70, 153, 154]

7.7. Umbilical blood samples and analysis (paper II and III)

Blood gas analysis:

Blood gas analysis were performed according to the department's standard procedures which included base excess (BE) (Radiometer, ABL 520, Lillestrøm, Norway).[155] Lactate was not measured.[156]

Metabolism of remifentanil in neonate:

Blood samples for remifentanil were analyzed by Eurofins Medinet B.V, Breda, Netherlands. Before analysis the following procedure was performed: collected blood samples were immediately transferred to tubes containing citrate. Blood and citrate were mixed before the tubes were stored in a freezer with temperature of -18°C or lower. Dry ice was used for transport of the remifentanil assays to the laboratory. The assay method is based on tandem mass spectrometry detection (LC–MS/MS).[157, 158]

7.8. Statistical analysis

SPSS version 16.0 for Windows / PASW Statistics 18 (IBM, Armonk, NY, USA) was used for data analysis. Statistical analysis of continuous data was performed by summary statistics, independent t-test, paired t-test, and Mann-Whitney U-test. For categorical data Pearson Chi-Square test and Fisher's exact test were used as appropriate. Data was presented as mean (SD) if not other specified, P-values < 0.05 were considered statistic significant for comparison of groups. Mixed linear modelling (30-240 minutes) was used to analyze longitudinal data on maternal pain, including a linear term for time. In paper II, this also included fixed effects for baseline pain, parity, age, BMI, supplemental oxygen and remifentanil doses. The model takes into account repeated measures for each parturient, and the varying number of women still in labour at different time-points measured. In paper II parturients of mixed parity were consecutively included during a 17 months period. In paper III, the prospective power calculation estimated a need for 26 patients in the epidural group and 26 patients in the remifentanil group (SD remifentanil group=20 millimeters, SD epidural group=30 millimeters) with a power of 80% at a significance level of 5%.[136, 139] Based on excisting evidence, significant pain reduction (VAS) was set to minimum 20 millimeters.[159]

7.9. Approvals and ethics

The project has been approved by The Regional Ethical Committee (Western Norway Regional Health Authority), Statens Legemiddelverk (Norwegian Medicines Agency) and NSD (The Data Inspectorate) / Datatilsynet (Supervisory Authority**)**. Unexpected or serious side effects were to be reported to Statens legemiddelverk (Norwegian Medicines Agency) (paper II and III).

Ethical aspects have been focused throughout the study because it involves both mother and fetus/newborn, and the research has been performed in a special clinical setting (labour and delivery).

There has been no support from - or contact with - pharmaceutical industry, and there were no conflicts of interest.

8. Summary of papers

Paper I

In paper I, the practice of labour analgesia in Norwegian hospitals were explored, especially their use of systemic opioids. During the last two decades, epidural analgesia has become "the gold standard" for labour pain in most Western countries. Newer short-acting opioids given systemically may represent an alternative for adequate pain relief without using regional techniques. To explore current practice in Norway, a questionnaire was sent to the head of all 46 registered labour units in 2005. The questionnaire focused on epidural and the use of systemic opioids. In 2008, the same questionnaire was sent to the 19 largest units reporting <1000 births a year, seeking updated information. Forthy-three of the 46 original questionnaires were returned. An epidural frequency of 25.9% was registered. For epidural treatment, bupivacaine was the preferred local anaesthetic, while sufentanil was the opioid of choice for the majority of units. Pethidine was the most commonly used opioid for systemic administration (77%). A few units used morphine, only one unit used IV fentanyl. All units reported nurse administration of systemic opioids. The IM route was most commonly used, either alone (58%) or in combination with an intravenous administration (34%). There were only minor changes with the repeated survey, except for one large unit, which reported a 50% increase in the epidural frequency. The study concludes that the frequency of epidural for labour analgesia is still relatively low in Norway, but seems to be increasing. Systemic opioids are often used instead of or as a supplement. Clinical practice seems to be conservative, and newer short-acting opioids are seldom used systemically.

Paper II

Remifentanil seems to have a suitable pharmacological profile for labour analgesia. But the evidence so far is limited, and the need for more studies has been emphasized. In a prospective, observational study we examined intravenous patient-controlled analgesia used as stepwise bolus doses. Primary outcomes were pain reduction and maternal satisfaction. We also investigated maternal and early neonatal side effects, and metabolism of remifentanil in

the neonate. Parturients with normal term singleton pregnancies were recruited. Starting bolus dose was 0.15 $\mu g \cdot kg^{-1}$, with increasing dose steps of 0.15 $\mu g \cdot kg^{-1}$ and lock-out time two minutes. Pain scores were recorded every 15.minute using a 100 mm visual analogue scale (VAS). Maternal oxygen saturation (SaO_2) and heart rate (HR) were monitored continuously. Systolic and diastolic blood pressure, respiratory rate (RR) and maternal sedation were recorded every 15.minute. Supplemental oxygen was administrated if SaO_2<92%. Neonatal data included Apgar scores, clinical examination, naloxone use, resuscitation, umbilical blood gases and umbilical remifentanil concentrations. Forty one parturients were enrolled, duration of analgesia was mean 216 (range 68-439) minutes. Pain scores (VAS) were significantly reduced the first 3 hours of therapy. Maximal measured pain reduction was average 60% compared to baseline. Doses varied between 0.15-1.05 $\mu g \cdot kg^{-1}$. Thirty-seven (93%) reported satisfaction with analgesia. Lowest SaO_2 and RR were 91% and 9 $\cdot min^{-1}$, respectively. Supplemental oxygen was administrated to 11 parturients (27%), the level of maternal sedation was moderate. Neonatal data were reassuring. The study concludes that remifentanil as IVPCA bolus doses gives adequate pain relief and high maternal satisfaction. Sedation and ventilatory depression may occur, but no serious neonatal side effects were registered. Careful monitoring is mandatory.

Paper III

Based on the satisfactory results in paper II, we compared the analgesic efficacy and side effects of remifentanil IVPCA with standard epidural analgesia during labour. Thirty-nine parturients with normal singleton pregnancies and of mixed parity were randomized to receive either remifentanil IVPCA (RA group), or epidural analgesia (EA group). The epidural solution contained ropivacain 1 $mg \cdot ml^{-1}$ and fentanyl 2 $\mu g \cdot ml^{-1}$, initial infusion dose was 10 $ml \cdot h^{-1}$. Starting bolus dose of remifentanil was 0.15 $\mu g \cdot kg^{-1}$, with increasing dose steps of 0.15 $\mu g \cdot kg^{-1}$. Lock-out time was 2 minutes, bolus infusion speed 2 $ml \cdot min^{-1}$ (100 $\mu g \cdot min^{-1}$) and without background infusion. Visual analogue scale (VAS) was used for pain assessment. Maternal heart rate, blood pressure, oxygen saturation, respiratory rate, sedation, nausea/vomiting, itching, satisfaction with analgesia and fetal/neonatal outcome were recorded. Thirty-nine parturients of mixed parity were enrolled, inclusion was stopped at this number because of technical problems with the IVPCA pumps (EA group 20, RA group 37).

Thirty-seven parturients were included in analysis. Both remifentanil and epidural reduced pain effectively, with no significant differences (p=0.366) between the groups during the study period. Pain reduction at end of first and second stage, and maximum pain reduction, was similar (RA/EA): 27/26mm (p=0.920), 31/29mm (p=0.909) and 61/59mm (p=0.855). There was no difference between the groups regarding satisfaction. One parturient receiving remifentanil (6%) were converted to epidural because of inadequate analgesia. Remifentanil produced more sedation, desaturation (SaO_2<92%) and need for supplemental oxygen. Fetal and neonatal outcome was reassuring. Highest mean dose of remifentanil was 0.70 (0.30-1.05) $\mu g \cdot kg^{-1}$. Parturients receiving epidural analgesia reported some better pain scores compared to remifentanil IVPCA, but all differences were non-significant.

The study concludes that remifenanil produces effective analgesia comparable with EDA, with high satisfaction scores and reassuring neonatal outcome. There is a higher risk for sedation and desaturation, therefore close monitoring is mandatory.

9. General discussion

9.1. Methodology

Surveys

Good clinical practice should mainly be based on updated scientific evidence and recommendations, but can sometimes be influenced by other factors like traditions and culture. If clinical recommendations and procedures are not in accordance with the available guidelines, changes in clinical practice should be considered. If need for updated information regarding current practice, a national survey is a recommended scientific approach. This method gives the opportunity to compare own practice with other hospitals, and to look for development and improved diagnostic and therapeutical options. Of course, despite standard questionnaires and accurate study procedures, survey results can be inaccurate and lack information. For example, the respondents can give different interpretations of the questions asked, or simply not give full and honest answers in some situations.[160]
Nevertheless, a survey can be a good scientific method to identify both future research topics and potential key points for improvement of clinical practice. One strength of the current survey is non-selected information on the topics investigated, as the respondents represent the real population we intended to study. All registered labour units in Norway in 2005 were included in the survey, with a response rate of 93.5%. A limitation of the 2005-questionnaire was that we did not ask specifically about other neuroaxial methods than EDA, or use of peripheral nerve blocks. The repeated survey from 2008 contained questions about neuroaxial blockades (spinal and CSE analgesia). Other limitations might be lack of questions for detailed protocols or dosing recommendations for systemic opioids, and that the questions were related to living births only.

Prospective observational studies

Implementation of new clinical methods and techniques should be based on scientific evidence. The ideal, high quality, clinical trial includes randomization, blinding, control group, sufficient power and trial size, and adequate size of effects to be clinical important. In clinical medicine, such controlled studies can sometimes be difficult to perform, because of practical reasons or ethical concerns, and observational studies might be the most suitable design to use.[46, 52] Although observational studies might be biased (for instace by selection, or observervation parameters), this method is important to bring scientific documentation by systematic continuous registration of effects and side effects, for example in a new field of research and practice.

Our department has about 2000 deliveries per year. The parturients were consecutively included from our daily clinical practice (paper II), the results of the study should therefore be valid also for other hospitals, event though the number of included patients was not very high. To perform large and well designed studies of remifentanil labour analgesia is challenging, because of the resources needed, it is time consuming and occupies skilled personnel for long periods (observing anaesthesiologist and midwives).

To increase the study population, we chose an observational study design and included both primi- and multipareous. Even though the study was possibly underpowered to draw conclusions on neonatal outcome and safety, as serum concentrations of remifentanil were analyzed from a limited number of umbilical cords. The complex techniques and prosedures to secure quality of these samples were the main reasons for the limited number analyzed. The chosen study design also has some other limitiations; it could be biased by selecting subjects positive to try systemic opioid analgesia, previous childbirths may influence the parturients evaluation, and lower the risk of obstetric intervention. We did not have a systematic registration of nausea/vomiting and itching with baseline values. Finally, registration of end tidal CO_2 could have given valuable additional ventilatory information, as hypoventilation could be detected earlier than by monitoring just oxygen saturation and respiratory rate.[161]

Randomized, double blind trials

For clinical research, randomized trials are the preferred design, and known to be the "gold standard" method. By this design, with a calculated number of participants to give sufficient power, it is possible to reveal even small differences in measured parameters. But to be of interest for clinicians in daily practice, such differences must be of clinical relevance. In addition, randomized clinical trials are normally designed for evaluation of defined end points (efficacy, side effects). They are usually not designed to detect infrequent side effects. Blinding of patient and/or investigator can be used to strengthen the results of a study. Nevertheless, even such well-designed studies are based on a selection of patients, and thus not automatically transferable to daily clinical practice.

Our study of remifentanil IVPCA compared to EDA (paper III) was not blinded. Of course, this could give biased results, but we found blinding to be ethical doubtful and too demanding.[52] As already mentioned, we might have strengthened the study by monitoring end tidal CO_2, and collecting information about nausea/vomiting and itching before start. The prospective sample size calculation considered pain reduction, and did not consider side effects. After inclusion of 39 patients we had a technical problem with our remifentanil infusion pump, but as we were so near the calculated sample size, we decided to stop inclusion, instad of finding another pump with other technical specifications that could influence the results.

9.2. Changes in pharmacological labour analgesia in Norway, especially the use of parenteral opioids and epidural.

Epidural is shown to be the most effective analgesia method for women in labour, and the EDA-frequency has increased markedly the last two decades in the Western world, including Norway. Pethidine has been the opioid of choice for systemic labour analgesia in most Norwegian labour wards, and this preference has been stable for several decades, even though criticism have been raised; claiming that pethidine is more sedative than analgesic, and therefore should not be used. Many departments also use nitrous oxide inhalation to alleviate labour pain, either alone or in combination with pethidine, despite the increasing warnings regarding pollution and environmental concerns. Several studies have shown that both pethidin and N_2O give only modest analgesia.[19, 20, 38, 98, 102, 103, 138, 141, 145]
There is obviously need for a change to offer an efficient alternative to the parturients that may not be able to use an epidural. Newer, short-acting systemic opioids have a more suitable pharmacological profile for pain relief during labour and delivery. Clinical studies have demonstrated analgesic efficacy, however, the maternal side effects have been a problem.
On this background, we conducted a survey to evaluate the pharmacological methods used for labour analgesia in Norway. Opioids and routes of administration were specially focused.
The results indicate that EDA was used by one-fourth of all parturients. We found that pethidine was the most used parenteral opioid, followed by morphine. One obstetric department used fentanyl and two used remifentanil in 2008. IM administration of systemic opioids was widely used.

<u>Neuraxial labour analgesia</u>

The frequency of EDA was found to be comparable with the results from a previous Norwegian study, and the frequency seems to be increasing.[13, 43] Compared with many other Western countries the frequency is still low.[3, 7, 9, 21, 44] This is surprising in a country with one of the world's highest income per citizen, and with a well-developed public health care system. This low frequency of epidural may partly be explained by the way labour service is organized in Norway. Only level 1 and level 2 have resources to provide an epidural service

to the parturients. Level l units and the majority of level 2 units offer this as a 24 h service. In the level 1 units, epidurals were provided to about 30% of parturients, and for level 2 units the average epidural frequency was about 20%. Level 3 units (called 'fødestuer', midwife-led delivery units) have a midwife service, but without obstetrician, anaesthesiologist or paediatrician available.[152] These units, however, represent only 1% of the annual deliveries. With this differentiated and decentralized labour service, it is important to have effective and safe pain relief alternatives. Even though EDA is regarded to be both effective and safe, not all women may be given this treatment. The procedure can be contraindicated, impossible to perform or unwanted by the parturient. Caesarean section rates were earlier thought to be increased by an epidural; today, there is no evidence indicating such an increase.[44] However, as for all invasive procedures, possible negative effects have to be evaluated before starting an epidural.

Sufentanil was the most commonly used opioid for EDA, especially in level 2 units. In the larger units (level 1), fentanyl was used as frequently as sufentanil. The results may indicate that the larger units have a more conservative attitude concerning epidural opioids. This may also reflect different opinions; some experts regarding sufentanil as a safer drug than fentanyl, while others concluding that the two opioids are equally safe.[55, 74, 93, 162, 163]

Bupivacaine was the preferred local anaesthetic component of the epidural solution (56%), followed by ropivacaine (39%). One ward reported the use of PCEA.

The design of the survey did not explore regional techniques other than EDA. Information collected indicated some limited use of spinal- and/or CSE analgesia, but the total number was small, and comparable with a previous Norwegian study.[13] CSE is commonly used in many Western countries today, and by many thought to combine the advantages of both epidural- and spinal techniques. A Cochrane review in 2012 compared CSE with both high- and low-dose EDA for labour regarding efficacy and safety. They found CSE to have slightly faster onset of pain relief, but produced more itching compared to EDA. There were no differences in maternal satisfaction, mobility in labour, headaches, Caesarean section or fetal/neonatal side effects. Overall, they found little difference between the two techniques.[49] In our surveys, we did not record data on peripheral nerve blocks.

Systemic labour analgesia: Opioids and nitrous oxide

According to the performed surveys, systemic opioids are widely used for pain relief during labour. Pethidine is still the most frequently used opioid in Norway, even though side effects have been extensively discussed.[13, 14] Several studies have concluded that other opioids have better analgesic effects and less side effects, and the analgesic efficacy of pethidine has thus been questioned.[14, 20, 110] A recent Cochrane review[5] on 54 studies including over 7000 parturients evaluated parenteral opioids for maternal pain relief in labour. The review concluded that, parenteral opioids provided some pain relief, but for most outcomes there were no significant differences between the different opioids. There were no good studies on opioid safety, thus the assessment of safety was poor.

In our two surveys we found that some units used morphine, and the use seemed to increase according to the repeated survey in 2008. Morphine has a shorter half-life and a more rapid plasma clearance than pethidine in pregnant women, and may thus be a better alternative. However, there are few studies evaluating the analgesic effect and side effects of morphine during labour. Both morphine and pethidine have active metabolites, nor-pethidine being the most worrying concerning neonatal side effects.[13, 14, 17, 26, 113]

Since 2005 our hospital has replaced pethidine with IV fentanyl as the routine opioid method for treating labour pain. No other Norwegian hospital reported the use of fentanyl, even though fentanyl has been used for pain relief during labour in several other Western countries. It has been shown to have potent analgesic effects on labour pain and acceptable side effects.[17, 22, 26]

Our own experience with fentanyl so far is very positive. Compared with other similar hospitals in Norway, the epidural frequency is low. Our experience is that we often succeed in controlling the labour pain by using fentanyl.[17, 142] Results from the first year of fentanyl labour analgesia, indicate pain reduction (VAS score) and maternal satisfaction with analgesia, so far without reports of serious side effects (unpublished data).

The survey indicates that the use of opioids for labour pain in Norway seems to be based more on traditions, than evidence-based knowledge. According to available evidence, the use of pethidine and morphine to parturients should be reconsidered and reduced. The frequent use of nitrous oxide is also questionable, and remifentanil has been demonstrated to provide better analgesia than nitrous oxide.[145] Recent publications have demonstrated changes in the use of

systemic opioids in many countries. Fentanyl, alfentanil, sufentanil and remifentanil are used as systemic labour analgesics in several Western countries.[15, 28] These newer opioids may provide better analgesia, but their possible side effects have to be monitored carefully, and further studies on safety and efficacy are needed.[27, 164]

The majority of the responders used IM administration of opioids, either alone or in combination with IV administration. No wards on level 3 reported use of IV administration. Units on levels 2 and 3 more frequently used the IM route alone compared with level 1. It is surprising that so many labour units still use IM administration. From a pharmacological point of view, the IV route is preferable. It is easier to control, and titrate to optimal effect.[17, 165]

The use of short-acting opioids with a fast onset is preferable. Some studies have pointed out that opioids should be delivered as IVPCA.[15, 22] This may optimize pain relief, reduce the total dose required and cause less side effects. However, other studies have not demonstrated any difference between IVPCA and nurse-administrated IV analgesia with respect to these issues.[23] Our study demonstrates that Norwegian labour units do not offer patient-controlled analgesia to the parturients. Nurse-administered systemic opioids thus seem to be the most common method used in Norwegian labour wards. The number of patients receiving such analgesia varied, from 1% up to nearly half of the vaginal births (44%). Several responding units reported imprecise registration of labour analgesics; four units answered that they did not have reliable statistics on the use of systemic opioids. This is a major concern; as registration of such clinical data should be performed continuously. This form of documentation is mandatory both for medical and legal purposes.

Resources and health economics

For EDA, extra resources are required compared with traditional systemic pharmacological methods for pain relief. Increased epidural costs are due to both the professional resources needed and the increased complication costs, even though the methods for estimating costs have been discussed.[43, 52, 162, 166-169]

The use of a potent opioid as remifentanil for labour analgesia require close monitoring and one-to-one midwifery, by this increasing the need for resources and personell compared to the use of other systemic opioids. Continuous presence of a competent person during labour (a doula) has been demonstrated to have positive effects on the labour process per see; reducing the need for pharmacological analgesia as EDA, and also reducing the frequency of Caesarean section and instrumentanl delivery, in addition to better coping and less tension for the parturient.[52, 170-172] Therefore, by the use of one-to-one midwifery the real total costs of remifentanil IVPCA labour analgesia may be lower than demonstrated by an isolated economical calculation.

Conclusion

Labour analgesia in Norway seems to be based on conservative traditions.

Nitrous oxide is frequently used, as well as systemic use of pethidine and morphine. Newer opioids were very seldom used. Epidural frequency is rather low compared with other Western countries. Bupivacaine combined with fentanyl was the most frequent epidural solution used. A continuous fixed infusion was preferred, and some offer boluses given by a midwife. Only two hospitals had experience with newer opioids for IV labour analgesia.

9.3. Efficacy and safety of remifentanil IVPCA for pain relief during labour, including metabolism of remifentanil in the neonate.

The analgesic efficacy of traditional systemic opioids, like pethidine and morphine, has been questioned, and studies of remifentanil IVPCA have demonstrated promising results regarding labour pain reduction. In this prospective observational study, using a stepwise IVPCA bolus dosing regimen, remifentanil gave an overall significant reduction in pain score during the whole labour period including delivery. The method was assessed as clinically effective by the parturients, 88% would choose the same analgesia for their next labour. The highest doses (>0.75 $\mu g \cdot kg^{-1}$) seemed to induce moderate maternal sedation and respiratory depression, and some nausea/vomiting, but without need for medical action. These findings are in accordance with comparable studies where remfentanil seems to have better analgesic efficacy than both pethidine and nitrous oxide, although not as effective as epidural analgesia.[137, 141, 142, 145] In a recent randomized study by Douma et al, they found remifentanil to provide better analgesia than both fentanyl and pethidine.[38]

Dosing regimen

In previous studies, both continuous infusion, bolus doses, or a combination of these two methods have been used.[38, 135-137, 147] In the present studies, we used a stepwise and adjustable dosing regimen. We found IVPCA bolus doses, without background infusion, to be a suitable administration method to utilize the unique pharmacokinetic properties of remifentanil.[27, 135-139] Dose steps of 0.15 $\mu g \cdot kg^{-1}$ gave the possibility to titrate remifentanil to find the optimal dose, and individualize the pain therapy.

Some authors have recommended lean body mass for calculating the remifentanil dose.[173] The main reason for this recommendation is the low distribution volume for remifentanil (0.3-0.4 l/kg) which means that it is only distributed to the most active and central parts of the body. We therefore used a simple “lean-body mass” formula (bodyweight=body height minus 100), to avoid overdosing, although comparable studies have used total body weight.[24, 135-137, 139] We found the real total body weight to be nearly 20% higher than estimated weight, thus we recommend this method for calculating remifentanil doses to avoid overdosing.

With this approximation, the mean dose after one hour was 0.38 (0.14) $\mu g \cdot kg^{-1}$, which increased to 0.64 (0.20) at the end of stage 1. The mean maximal dose needed was 0.70 $\mu g \cdot kg^{-1}$, although three participants needed 1.05 $\mu g \cdot kg^{-1}$. This mean maximal dose is lower than Evron and colleagues found in a previous study, where the mean maximum dose was 0.93 $\mu g \cdot kg^{-1}$. A similar study from Finland concluded that the effective dose was 0.4 $\mu g \cdot kg^{-1}$, but this study had a duration of only 60 minutes.[137, 139] We observed large variations in dose between individuals. This is a well known characteristic of systemic opioids, explained by genetic variations and different tolerance for pain.[1, 24, 25, 137, 139, 174] With continuous monitoring, clinical observation (midwife, anaesthesiologist), and the criteria for handling of side effects, our dosing regimen with no maximal dose was found to be safe.

The time interval from end of analgesia to delivery was wide; two parturients had remifentanil stopped early because of conversion to epidural analgesia and later Caesarean section. For one parturient remifentanil was continued 3 minutes after delivery (placenta problems).

Analgesic efficacy: Pain scores and satisfaction

The average maximal pain reduction measured was 60% (47 millimeters) in our study ($p<0.01$). VAS pain scores were significant reduced the first 3 hours of analgesia, with a slight increase late in labour. This pattern in pain relief is known from previous studies.[24, 135, 139, 142] But even at very painful stages during labour, the scores were lower than baseline. The slow increase in pain scores cannot be explained by failed analgesia as pain scores are known to increase as labour progress.[38] Nevertheless, at end of first (full cervical opening) and second stage pain scores were significantly reduced ($p<0.05$). Average VAS scores measured at these clinical stages of childbirth were 63 and 64 millimeters, respectively. The maternal satisfaction scores in the current study were high, and this combination with sub-optimal pain reduction is well known, and consistent with conclusions from other authors.[135, 139, 175]

It could be argued that the average pain scores late in labour are based on a too low number of participants, but this is also known from other studies of remifentanil. The rate of conversion to epidural is low compared to other studies,[24, 27, 136] and only one patient in our study requested conversion to epidural analgesia because of inadequate pain relief. Unfortunately, she did not answer the questionnaire after delivery. A recent observational study by D'Onofrio et al demonstrated similar pain reduction and high satisfaction scores by use of

continuous IV infusion of remifentanil. However, pain scores were only reported for the first 30 minutes, and cross over to epidural was not an option if insufficient analgesia occurred.[147]

Maternal side effects

Respiratory depression is a feared opioid side effect.[27, 134, 137, 144, 175] By continuous monitoring and close clinical observation we registered no SaO_2 lower than 91%, and no RR lower than 9 breaths·min^{-1}. Supplemental oxygen was administered immediately when SaO_2 of 92% were observed (11/41), by this avoiding hypoxemia and giving the possibility to continue satisfactory analgesia. Also, because of frequent uterine contractions stimulating maternal ventilation, ventilatory depression seems to be self-limiting. Even with the highest doses of remifentanil, the respiratory data were acceptable.[176-179] As remifentanil is known to be a potent respiratory depressant, careful monitoring of ventilation is mandatory.[38]

Maternal sedation is an important side effect of IVPCA remifentanil, and different sedation scales have been used to assess the clinical implication. In the current study (paper II), the sedation scores by observer were based on a five-point verbal rating scale known to the midwives and anaesthesiologist involved. In this context, common understanding of key concepts and native language was found to be crucial. In addition, we miss validated international sedation scales designed especially for obstetric use. In our study observer scores were moderate and acceptable. One of the parturient reached a maximum score of 4 out of 5, but this was immediately reversed by stopping the PCA pump. All subjects could easily be aroused by verbal stimulation. The periods between uterine contractions present special risk for sedation, therefore continuous monitoring is warranted.[24, 135, 137, 139, 140] Different approaches have been tried to reduce this problem. In a recent study remifentanil bolus doses were administrated during the uterine contraction pause, resulting in slightly reduced sedation but no improved analgesia.[180]

Pulmonary aspiration and pneumonitis is a rare, but feared complication associated with general anesthesia to parturients. With severe drowsiness during parenteral opioid labour analgesia, one should be aware of the potential risk for pulmonary aspiration of gastric content. Although this is a rare complication, passive regurgitation might occur.[5, 101]

Very few parturients reported loss of memory, and sedation was described as a positive experience. To our knowledge, the positive experience of sedation during remifentanil labour analgesia has not been focused in previous studies. Only parturients with systematic registrations throughout labour were included in these analysis.

Nausea and vomiting are well known side effects of all opioids, including remifentanil.[134, 136, 138] One third of the subjects in our population reported mild nausea or vomiting without need for antiemetic medication. This is consistent with the results in other studies.[24, 137, 139]

Itching may be a troublesome side effect of opioids. In our study three parturients reported itching, but there was no need for medical treatment, which is in accordance with other researchers.[134, 135, 137]

Chest wall rigigity was not observed, although this has been reported by others regarding neonates.[181]

Fetal and neonatal monitoring

We used continuous monitoring of fetal heart rate (FHR) throughout the study period. FHR-changes were evaluated according to standard obstetric criteria used by the department (CTG, STAN). There were only minor FRH changes, as also found by others.[24, 135-137]

Apgar scores were within normal range, suggesting little neonatal risk using remifentanil in given doses close up till delivery. One minute after delivery four neonates had an Apgar score < 8. The lowest registered was 6, this was a primiparous with slow labour progression and need for mechanical delivery help. Our results are consistent with comparable studies regarding Apgar scores.[22, 24, 135-137, 141]

Also in accordance with similar studies, we found no significant change in umbilical blood gases,[24, 135-137] or any effect on the babies with routine paediatric examination.[24]

Umbilical remifentanil concentrations

It is known that remifentanil readily crosses the placenta.[24, 122, 146] The arterial and venous serum concentrations detected, and the calculated ratios of remifentanil and its metabolite,

indicate that mean bolus doses of 0.40 $\mu g \cdot kg^{-1}$ close up to delivery are rapidly metabolized or redistributed in the neonate with no accumulation.

We collected umbilical blood samples from 17 umbilical cords to determine remifentanil concentrations, including metabolite analysis. Because of initial analytical problems, a technical challenging procedure, and short time available after labour, we did not get valid samples from all the umbilical cords. But as far as we know, this is still among the largest such samples published so far.[24, 122]

Conclusion

With the mode of administration and dosing regimen in this study, remifentanil in dose range 0.15-1.05 $\mu g \cdot kg^{-1}$ gives satisfactory analgesia, with significant reduction in pain scores, and acceptable maternal and fetal side effects during labour and delivery. We advocate an adjustable IVPCA bolus dose regimen with dose steps of 0.15 $\mu g \cdot kg^{-1}$, and lock out time of two minutes. A wide range in dose requirement necessitates close titration of dose to individualize analgesia as labour progress.[164, 182]

Such a potent opioid may require increased resources and warrants clinical observations by skilled personnel, one-to-one midwifery, continuous monitoring and anaesthesiologist immediately available. Especially maternal sedation and ventilatory depression should be monitored, and liberal administration of supplemental oxygen is recommended.

Even though remifentanil crosses the placenta, it is rapidly redistributed and metabolized and seemed to give minimal risk of neonatal side effects. Remifentanil can be started in low doses early in labour, and may be used as an alternative to regional analgesia.

9.4. Remifentanil IVPCA compared with epidural analgesia with ropivacain and fentanyl; efficacy and safety during labour.

Epidural is widely used and the preferred method for alleviation of labour pain.[182] But for the group of parturients who cannot receive EDA, there should be effective and safe analgesia alternatives.[175] In the current prospective randomized, controlled study both remifentanil and epidural reduced pain effectively, with no overall significant differences in pain reduction between the groups. Despite the fact that VAS scores seemed to be some lower in the EA group during the period measured, there were no significant differences compared to remifentanil. The reduction in pain score was similar at the end of first and second stage, which are clinical stages of labour known to be very painful. Maximum pain reduction and satisfaction scores were comparable between the two treatmen groups. Maternal sedation and oxygen desaturation was more common in the RA group. Umbilical cord blood gas values tended to be some lower after remifenanil therapy, but clinical neonatal outcome was reassuring.

Pain reduction and satisfaction

Pain reduction was more pronounced initially in both groups. After 2 hours, pain scores in the RA group increased slightly. This pattern in pain score is well known from previous studies of remifentanil.[24, 38, 135, 139, 142, 145] There were no significant differences in pain reduction between the groups at the time-points measured, or overall for the whole study period (p=0.366). Even though, epidural tended to be slightly more effective than remifentanil IVPCA.

Our results indicate analgesic efficacy of remifentanil also during second stage of labour. Most previous studies have focused pain reduction during first stage.[12, 136] As discussed in chapter 9.3; it should be underlined that higher pain scores as labour progress, can be related to increased uterine contraction pain, and not explained by poor pain relief.[38]

One could argue that our average pain scores in late phases of labour are based on too low number of participants. This is a well known limitation from previous remifentanil studies.[38, 136, 144]

One parturient in the RA group was converted to epidural because of inadequate analgesia, this is a low failure rate compared with other studies.[12, 27, 38]
Regarding maternal satisfaction, 76% in the RA-group and 75% in the EDA-group reported to be very satisfied with analgesia. 94% in the RA-group and 90% in the EDA-group would choose the same labour analgesia method in the future.
The results from our study are convincing regarding remifentanil analgesia, with even better analgesic efficacy than demonstrated by Volmanen and colleagues.[142] The remifentanil pca dosing were weight-adjusted, using estimated bodyweight (formula: patient body height minus 100 = estimated weight, kg) as recommended.[173] Based on recommentatins from current literature, we chose to use intermittent bolus doses with no background infusion.[136, 139] Highest mean dose was 0.70 (range 0.3-1.05) $\mu g \cdot kg^{-1}$, at end of first and second stage the doses were 0.65 and 0.38 $\mu g \cdot kg^{-1}$. The mean dose at 1 hour was 0.40 (range 0.15-0.60) $\mu g \cdot kg^{-1}$. Some previous studies have used similar doses,[24, 137, 142] others have used lower doses and still demonstrated analgesic effect.[136, 138, 139] Dosing levels of 0.75 $\mu g \cdot kg^{-1}$ or more have been related to a higher risk for maternal oxygen desaturation and sedation. Because of individual variation in opioid respons,[139, 174] even doses of 0.3-0.45 $\mu g \cdot kg^{-1}$ could give side effects. Based on our body weight estimate, the maximum dose 1.05 $\mu g \cdot kg^{-1}$ is not higher than maximum doses used by others.[12]

Maternal side effects

We observed oxygen desaturation (<92%) and need for supplemental oxygen in 11 parturients in the RA group, no patients receiving EDA needed oxygen. Respiratory frequency lower than 9 was not registered. All parturients responded to verbal stimulation, being able to take deep breaths and restore normal SaO_2. It should be emphasized that oxygen was given immediately if SaO_2<92%, our protocol for handling of respiratory depression was found to be safe.[12, 38] In addition, ventilatory depression seems to be self-limiting because of frequent painful uterine contractions, stimulating the parturients ventilation. Our results are consistent with several remifentanil studies.[136, 138-140, 142] Volikas and colleagues did not find any desaturation among 50 women receiving remifentanil up to 0.5 $\mu g \cdot kg^{-1}$.[24] We found continuous pulse oxymetri and close clinical observation by skilled personnel to be mandatory, and recommend liberal administration of supplemental oxygen.

Sedation observer scores were significant higher in the remifentanil group after 1 hour and and end of first stage. Eleven from the RA group and two from the EA group reached a score of 3 (drowsy) as the highest, one receiving remifentanil had a highest score of 4 (very drowsy). All patients in the RA group experienced sedation, compared to 55% of the EA group. This is in agreement with other studies.[24, 135, 140, 142, 145]

Comparing of maternal sedation in different remifentanil studies is hindered by the use of various sedation scales. In the current study we chose to use a five-point verbal rating scale, this issue is further discussed in Chapter 9.3 (maternal side effects). The global sedation scores by parturient and attending midwife were comparable. Only one patient (EA group) reported sedation to be associated with discomfort. Nevertheless, the RA group had a higher level of sedation and more respiratory depression than parturients receiving EDA, especially with the highest remifentanil dosing levels. In daily clinical practice, often with limited personnel- and monitoring resources, we recommend that the maximum dose of 0.70 $\mu g \cdot kg^{-1}$ should not be exceeded regarding safety issues.

There were some more reports of vomiting in the RA group, but the difference was not significant. In some previous remifentanil studies the frequency of nausea has been low,[24, 137] others have concluded different.[135, 136, 138, 142]

Itching was reported by three patients in the EA group, which can be explained by systemic absorption of fentanyl from the epidural space.[69, 183] In a Cochrane review of neuraxial labour analgesia published in 2012, they found itching to be a possible opioid side effect, and more frequently associated with CSE than EDA.[49]

Fetal and neonatal side effects

Pathological FHR changes were registered for two patients in the RA group and one in the EDA group, all related to obstetric problems. The results are consistent with several studies of remifentanil.[27, 135-137, 140] Volmanen and collegues found similar FHR changes during epidural analgesia, but more abnormal FHR changes when receiving remifentanil.[142]

In the current study neonatal data were acceptable in both groups. Umbilical base excess and venous pH were lower in the RA group, but only the pH value being significant different ($p=0.043$). Our results are in accordance with previous literature,[24, 135-137, 139, 140] indicating

that remifentanil can be used until delivery without harm to the newborn. Remifentanil is known to cross placenta, and to be metabolized or redistributed in the neonate.[122]
Because of technical problems with the IVPCA pumps, we decided to stop inclusion of patients with a total number of 39 (EA group 20, RA group 19). This was close to the calculated number from the power analysis, and comparable to the previous study by Volmanen and colleagues regarding remifentanil and epidural.[142] Most previous remifentanil studies have a limited number of participants,[12, 24, 144] and larger studies evaluating safety and satisfaction has been a challenge so far.[24]

Conlusion

Epidural analgesia with ropivacain and fentanyl and remifentanil IVPCA had similar analgesic efficacy, and with no difference in overall satisfaction. Remifentanil produced significant more sedation and respiratory depression, with larger need for supplemental oxygen. Neonatal outcome was reassuring. Continuous close monitoring by trained personnel and one-to-one midwifery is mandatory, and liberal use of supplemental oxygen is recommended. Anesthesiologist should be immediately available. The doses should not exceed 0.7 $\mu g \cdot kg^{-1}$ with standard monitoring. Remifentanil IVPCA as a stepwise bolus dose regimen, with dose steps of 0.15 $\mu g \cdot kg^{-1}$ and lock-out time 2 min, can be used as alternative to epidural during labour and delivery. Remifentanil analgesia may not replace epidural, but could be an acceptable pain reduction method when epidural is not an option.

10. Main conclusions

Compared to other western countries, the epidural frequency in Norwegian labour wards is low, although it has increased significantly during the last decade. Nitrous oxide and traditional systemic opioids, like pethidine and morphine, are often used. The clinical practice seems conservative, newer short-acting opioids are seldom used.

Remifentanil administered as IVPCA gives effective pain relief, and can be used as analgesia method during labour and delivery. Maternal side effects, like sedation and ventilatory depression, were acceptable but require careful monitoring with anaesthesiologist immediately available. In analgesic doses, remifentanil does not give serious fetal or neonatal side effects, and is rapidly metabolized in the newborn.

Both EDA and remifentanil IVPCA reduced labour pain effectively, with high maternal satisfaction scores for both methods. Compared to EDA, remifentanil was associated with increased risk for maternal sedation and oxygen desaturation, and it is therefore mandatory with close monitoring and anesthesiologist available. Both remifentanil IVPCA and EDA seems safe for the neonate.

Based on the present study and excisting evidence, we recommend the use of IVPCA remifentanil as labour analgesia instead of traditional opioids as pethidine and morphine when EDA is not an option.

11. Future perspectives

Large, randomized multicenter trials are needed regarding remifentanil IVPCA labour analgesia; thus administration methods, dosing regimen, analgesic efficacy, maternal side effects, health economic issues and, personell resources needed should be further investigated. Maternal side effects like sedation and oxygen desaturation should have a special focus.[164, 175]

Based on previous studies and clinical experience, with close monitoring by skilled personnel and anesthesiologist immediately available, remifentanil can today be used in low doses during labour when indicated. Remifentanil seems to be beneficial for obstetric analgesia, and is already used in some countries.[9, 15, 175, 184] Because of the unique pharmacokinetic properties, remifentanil has the potential to be the parenteral opioid of choice for women in labour.

Even though EDA is a well established and safe procedure for labour pain, the use of spinal- and CSE analgesia in Norway needs to be further investigated.[49]

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