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Pain relief following cesarean section - short and long term perspectives

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In the memory of my grandfather Agr. Dr. Åke Nyhlén -

who proved that nothing is impossible and that it is never too late.

Grandpa defended his thesis in 1987, 80 years old.

ABSTRACT

Background Postoperative pain treatment in women undergoing cesarean section (CS) needs to be effective to enable fast and smooth recovery without adverse outcomes and to improve breastfeeding and bonding between mother and child. It is also important that pain treatment should have minimal impact on the newborn

The overall aim of this thesis was to investigate how to improve pain management in women undergoing cesarean section.

Specific aims were:

- To investigate if a single injection of bupivacaine with adrenaline close to the fascia could decrease opiate consumption and pain in patients undergoing CS in spinal anesthesia and whether the same treatment influences the need for opiates in women operated in general anesthesia (paper 1 and 3).
- To study the overall incidence and risk factors for persistent pain after CS and to characterize the persistent pain, regarding intensity, body location and impact on daily life (paper 2).
- To clarify whether oral oxycodone (OXY) can provide equal/better and safe postoperative pain relief after CS compared to intravenous morphine followed by oral codeine (IVM) (paper 4).
- To study pharmacokinetic aspects of postoperative OXY treatment of mothers after CS and to investigate possible drug exposure through breast milk, including the effects on the newborn (paper 5).

Methods and results:

Study I: Two hundred and sixty women undergoing CS were randomized to receive injection of either 40 ml bupivacaine (2.5 mg/ml) with adrenaline (5 µg/ml) (n=130) or 40 ml saline solution (0.9%) (n=130), close to the fascia before closure of the wound. Morphine consumption, pain assessment by Numerical Rating Scale (NRS) and time to mobilization were recorded. Morphine requirements were significantly less for up to 12 h postoperatively and mean and maximum pain intensity lower during the first 6 h in the group receiving local anesthesia ($p \leq 0.05$).

Study II: A prospective follow up study of the women participating in study I. A questionnaire consisting of the Brief Pain Inventory (BPI) was posted to all women at 3, 6 and 12 months after surgery. Women rated pain intensity as well as interference with factors related to general function and quality of life. Women reported pain in one or more locations, in the CS surgical site as well as in other parts of the body. At 3 months 40% had pain and at 6 and 12 months 27% and 21%, still had pain. CS on maternal request i.e. psychological indication as well as a first CS were significant ($p \leq 0.05$) risk factors for persistent pain at 3 months. Severe postoperative pain in the immediate postoperative period (0-48 h) or undergoing a first CS were significant independent risk factors for the development of persistent pain up to 6 months after CS. Parameters related to quality of life such as sleeping difficulties were significantly impaired in women with persistent pain.

Study III: A retrospective study (2008-2014) was conducted at the Karolinska University Hospital, Huddinge where medical records of women who underwent CS in general anesthesia were reviewed. After applying exclusion criteria 250 medical records remained. Information

about women receiving local anesthesia in the surgical wound, 20 or 40 ml bupivacaine/adrenaline (36 and 42 women in each group), were collected and data from women receiving no local treatment were identified and served as controls (n=172). A significantly lower morphine consumption during the 6 first postoperative hours was seen in patients receiving 40 ml local anesthetics when compared with controls ($p \leq 0.05$) but no difference was seen for the 20 ml group or between treatment groups.

Study IV: Eighty women scheduled for elective CS were recruited and randomized to receive extended release tablets and short acting OXY (n=40) or IVM (n=40). All patients received a multimodal therapy with ibuprofen and paracetamol and the opiates were administered as needed. Outcome measures were safety parameters for mother and child, opioid requirements, pain intensity by NRS, time to mobilization and time consumption to administer drugs. To evaluate safety for the newborns Apgar scores, acid base status in the umbilical cord, weight development and the Neurological Adaptive Capacity Score were used. A significantly lower postoperative pain intensity measured by NRS was observed 0-6 hours and 25-48 hours in the OXY group ($p \leq 0.05$). Opioid consumption was significantly less in the OXY than in the IVM group 0-5 days postoperatively. Total time to administer analgesics was significantly shorter in the OXY group. There was a significant difference in common opiate related adverse effects between the two groups (3 women in the OXY group compared to 15 in the IVM/codeine group). No negative effects in the newborns related to opioid treatment were observed in either of the two groups.

Study V: The material was obtained in study IV. Maternal blood and breastmilk were sampled at 24 and 48 hours and neonatal blood was collected at 48 hours postpartum. All samples were analyzed for OXY and the metabolites noroxycodone, oxymorphone and noroxymorphone. Detectable plasma levels of OXY and its metabolites were found in all women and even if there were small quantities of breastmilk detectable levels were found also here. In most cases there were low or non-detectable levels of OXY in the plasma of the neonates.

Conclusions: A single injection of bupivacaine with adrenaline in the surgical wound decreases the need for rescue morphine postoperatively and was demonstrated to be a safe and effective pain management in women undergoing CS both in spinal and general anesthesia. Standardized postoperative treatment with oral OXY after CS was shown to be time effective and to give a better pain control, with lower opioid intake than a protocol using IVM/codeine, both as components of a multimodal analgesic regime. Our clinical data and the pharmacokinetic analyses support the view that OXY treatment is safe for mothers and neonates. As severe postoperative pain is a risk factor for long term pain the initial pain relief is crucial and we found that experiences related to quality of life were significantly impaired in women with persistent pain. We suggest that our findings can be of clinical importance, not least in women who have their CS performed in general anesthesia.

Keywords: pain management, local anesthesia, cesarean section, morphine consumption, postoperative pain, persistent pain, risk factors, quality of daily life, multimodal treatment, oxycodone, codeine, newborn, safety.

LIST OF PUBLICATIONS

I. Niklasson B, Börjesson A, Carmnes UB, Segerdahl M, Georgsson Öhman S, Blanck A. **Intraoperative injection of bupivacaine-adrenaline close to the fascia reduces morphine requirements after cesarean section: a randomized controlled trial.** Acta Obstet Gynecol Scand. 2012; 91(12):1433-9.

II. Niklasson B, Georgsson Öhman S, Segerdahl M, Blanck A. **Risk factors for persistent pain and the influence on maternal wellbeing after Cesarean section.** Acta Obstet Gynecol Scand 2015. Epub ahead of print.

III. Niklasson B, Molnar P, Blanck A. **A single dose of bupivacaine-adrenaline decreases opioid consumption after cesarean section in general anesthesia.** Manuscript.

IV. Niklasson B, Arnelo C, Georgsson Öhman S, Segerdahl M, Blanck A. **Oral oxycodone for pain after caesarean section: a randomized comparison with nurse-administered IV morphine in a pragmatic study.** Scandinavian Journal of Pain. 2015 Jan; 7: 17-24. Open access.

V. Segerdahl M, Niklasson B, Georgsson Öhman S, Blanck A, Boström E. **Oxycodone for postoperative pain control after Cesarean section: oxycodone and metabolites' distribution into breast milk and effect on neonate NACS score.** Manuscript.

CONTENTS

List of abbreviations

BMI	Body mass index
BMT	Breast milk transfer
BPI	Brief pain inventory
b.w.	Birth weight
CNS	Central nervous system
COX	Cyclooxygenase
CS	Cesarean section
i.v.	Intravenous
IVM/codeine	Intravenous morphine and codeine
NACS	Neurological and adaptive capacity score
NICU	Neonatal intensive care unit
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drugs
OXY	Oxycodone
PCA	Patient controlled analgesia
PK	Pharmacokinetics
SSC	Skin to skin contact
s.c.	Subcutaneous
TAP	Transversus abdominis plane blockade
WHO	World Health Organization

Definitions

Multimodal treatment	Treatment strategies which include a combination of different analgesic options such as regional techniques, opioids and non-opioid analgesics
Numerical Rating Scale	Numerical rating scale (NRS) is a numerical 10 cm scale 0-10 where 0 is “no pain” at all and 10 “worst pain”

1 INTRODUCTION

1.1 DEFINITION OF CESAREAN SECTION

A cesarean section is a surgical procedure in which an incision is made through abdomen and uterus to deliver a baby. Cesarean section is also called caesarean section, C-section, CS.

1.2 CESAREAN SECTION IN HISTORY

There are many different explanations for the origin of the word cesarean. One explanation could be that it derives from the Latin verb “caedare", meaning to cut [1].

Cesarean section was performed when there was no more hope for the mother. Either she was dying or already dead or it was the last chance to save the fetus. There were also religious laws forbidding the fetus to be buried in the womb of the mother, the fetus was cut out and buried beside the mother [1, 2].

During the renaissance CS was conducted on medical grounds. The first known successful CS, according to legend, was performed in the year 1500, by the sow gelder Jacob Nufer. He did the CS on his wife and it was said that she gave birth to more children after the operation. The CS baby that was born on this occasion lived a long life and died at the age of 77 [1-3].

The first documented and corroborated CS was performed 1610 on a woman in Germany. The women survived the CS but died 25 days later from an infection. The baby boy survived the surgery and lived until the age of nine.

The success of CS is defined from the outcome that the mother and fetus will survive for at least a month postoperatively. Successful CS was performed internationally for

the first time between 1826-1879, with one exception in 1792 when a CS was performed in the Netherlands on a women with a deformed pelvis [4].

1.3 CESAREAN SECTION TODAY

1.3.1 Cesarean section rate worldwide

A significant proportion of women giving birth undergo acute or planned CS. There are about 18.5 million CS deliveries performed every year globally (2008) [5].

The rate of CS has increased worldwide during the past decades, in Sweden from 5% in the mid 70ths to slightly more than 17% in 2013 [6]. This rate continues to rise and is in Europe approximately 20% [7] and in USA 33% [8]. The CS rate in certain areas in South America is nearly 50%, but there is a difference in the rates depending on the presence of private birth clinics or not [9]. In 1985 the World Health Organization (WHO) stated: "There is no justification for any region to have CS rates higher than 10-15%" [5]. A WHO report from 2010 states that countries with CS rates below 10% are considered underusing, while countries with rates above 15% are considered to overuse. A rate between 10%-15% was considered normal and 14 countries out of 137 were within this range. In the same report from 2010 the level of CS in Sweden was 17.3% with data from 2006. Brazil was in the top with a rate of 45.9% (2006) and Chad at the bottom with 0.4% (2004). Finland and Norway were slightly above 16% and Denmark had a CS rate of 21% [5]. According to the report from the Swedish Society of Obstetrics and Gynecology (ARG-report), 2010, the largest percentage of increase in CS between the years 1995-2001 was within the group "CS before onset of labor". Here an increase of 50% was observed in the group within single cephalic presentation. The frequency then remained unchanged for some years to increase in 2004 to 12.8% and reaching almost 14% in 2006. According to the ARG report risk factors for CS in the period 1995 to 2001 were primiparity, high

BMI, low education, smoking and being an immigrant. Moreover, it was seen that with increasing age the risk rose for CS. Women in the age group 35-40 were three times more likely to deliver by CS than those in the 20-25 year age group [10].

1.3.2 Indications for cesarean section

The main reason for performing CS is an immediate threat to the life of mother and/or fetus. The CS can be performed within different time frames depending on degree of urgency (and local routines), from decision to action: Immediate, emergency or elective, the last one before onset of labor [11, 12]. The indications for CS varies from absolute medical indications like placental abnormalities, antepartum hemorrhage, uterine rupture, obstructed pelvis, acute fetal distress, protracted labor, maternal/fetal diseases, multiple pregnancy or fetal malpresentation, to relative indications including maternal request [13]. The most common indications for CS in Sweden 1995-2006 were disproportion/dystocia (newborn weighing >4500 gr; with 34.2 %) and different kinds of fetal indications (31.7 %) [10].

1.3.3 Surgery – cesarean section

1.3.3.1 Surgical technique

The most used surgical technique in CS is the Joel-Cohen method, recommended by the WHO and discussed in the previously mentioned ARG report [10, 14]. The Joel-Cohen method includes a lower transverse abdominal incision with non-closure of both layers of the peritoneum and intracutaneous suture in the skin. A commentary from the WHO Reproductive Health Library [14] covers two Cochrane reviews [15, 16] which report that there are advantages for Joel-Cohen compared to the previously used Pfannenstiel incision with less postoperative morbidity, less need for analgesia, less blood loss, shorter surgery/delivery time and shorter hospital stay. With Joel-Cohen the abdomen is mainly opened bluntly, after the first sharp incision fingers are

used to separate the tissues. This is considered the explanation for the abovementioned advantages for the Joel-Cohen compared to the Pfannenstiel technique.

1.3.3.2 Intrathecal anesthesia

Spinal anesthesia is the method of choice for CS. If an elective CS, a majority of women undergo the surgery with intrathecal anesthetic techniques, mostly spinal anesthesia with local anesthetics and today often with addition of an opioid [17]. General anesthesia is mainly used when under time pressure (e.g. fetal distress) or due to medical contraindications to intrathecal anesthesia. The epidural and spinal techniques are known as regional techniques because pain relief is limited to a certain anatomical region. One substantial benefit of intrathecal anesthesia is a conscious mother who has the possibility to have skin-to-skin contact with the baby immediately after the baby is born. The woman's partner is also able to be present at the birth of the child. Another advantage of regional anesthesia is that relatively small doses of anesthetics are needed, with minimum side effects in the mother and the newborn. Intrathecal anesthesia is also a good start of effective pain relief, in combination with other drugs in the immediate postoperative period [18].

1.3.3.3 Local surgery routines: pre-, peri- and postoperatively

Preparations for CS in our setting follow strict procedures and premedication is normally given. According to local routines all women receive a bolus dose of 2 g paracetamol (Alvedon®) by oral administration one hour before any planned CS. Patients are fasting, get a peripheral venous catheter and a urinary catheter is inserted before going to surgery. The heartbeats of the fetus are monitored before surgery. Upon patient arrival in the operating theater all women get oral sodium citrate solution (30 ml). All patients receive a standardized intrathecal injection with

bupivacaine (Marcain® spinal tung) followed by fentanyl (Fentanyl®) in a sitting position. As a rule the other parent or another accompanying person is present during the CS. Skin-to-skin contact between mother and child is initiated as early as possible, often already in the operating theater. The mother stays in the recovery room until full recovery from the intrathecal injection and pain is manageable. The woman is preoperatively instructed about how to use the Numerical Rating Scale (NRS) to evaluate pain and pain management. The scale goes from 0, no pain at all, to 10 worst imaginable pain. Pain is generally treated from NRS ≥4 until NRS ≤3. Mobilization starts from approximately 5-6 hours after surgery, with the women sitting on the edge of the bed, standing next to bed and walking around in the room. Early feeding with lunch and/or dinner the same day as surgery is practiced. Normally the patient is discharged from hospital 2 days after a CS. Pre-, peri- and postoperative routines are based on evidence and follow such recommendations as stated by the Royal College of Obstetricians and Gynaecologists [12].

1.4 DEFINITION OF PAIN

The definition of pain by the International Association for the Study of Pain (IASP): "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [19].

1.5 PAIN MECHANISMS

Pain perception is multifactorial and a complex mixture of neural interactions that start with tissue damage (transduced and encoded by nociceptors), leading to activation of the ascending- and descending systems and a chain of events begins that involves both electrical and chemical activities. It is also activated by the influence of psychological and environmental factors [20-22]. Acute pain should therefore be viewed as the initiation phase of an extensive, persistent nociceptive and behavioral cascade most often triggered by tissue injury [21].

Acute pain is present as long as the input is relevant and fades when the damaging stimulus is removed. Postoperative pain after CS consists of two different pain sensations. First the somatic pain from the wound and secondly the visceral pain from the uterine contractions. Mechanisms transducing these pains are somewhat different, in that the somatic pain is well localized, while the visceral pain is sensed as more diffuse pain in the somatic wound normally wanes within 1-2 days, while the visceral pain components last for a few days longer [23].

When performing either the Pfannenstiel or the Joel Cohen incision the involved area is innervated by nerves from T11-T12. Nevertheless, the pain can also be derived from nerves outside this range as the skin is usually stretched and the internal organs manipulated during CS [17]. However, not only tissue damage but also psychological and sociodemographic factors are important factors behind patient's perception of pain [24]. Kehlet reports in a review from 2006 that: "Theories about the

development of chronic pain have shifted from a biomedical model to a biopsychosocial one, in which pain is thought to be the result of an interaction between biological and psychological variables" [23]. The mental representation of pain is stored as both short-term and long-term memory and serves as an early warning avoidance system for future threats. The important issue is the patients' perception/experience of pain [22].

1.5.1 Pain receptors

The pain receptors are involved in the defense of the body from the surroundings by reacting to damaging factors as tissue injury, chemical influence, heating and cooling which can pose a potential risk [20]. An external noxious stimulus starts a cascade of events that leads to activation of peripheral sensory neurons, C- and Aδ- nociceptors. Both the A- and C-δ fibers responds to painful stimuli, initiates and mediates pain impulses from both somatic and visceral tissue. There are proportionally more Aδ fibers in the skin and somatic tissue as they are needed to localize the pain and to protect the injured body part in order for it to heal and get restored. While there are proportionally more C-δ found in the viscera. Aδ -fibers lead the "fast" immediate pain through the first stimulus, while Cδ -fibers account for the subsequent continuous pain [20, 25].

A depolarization of the nerve cell occurs in connection with activation of the receptors, leading to an opening of sodium and calcium channels, resulting in sending a nerve impulse. At the same time inflammatory molecules as prostaglandins and bradykinins are released into the periphery and invoke an immune response activating and sensitizing the nociceptors and this also leads to a peripheral hyperalgesia reaction [26]. The definition of hyperalgesia is *increased* pain from a stimulus that normally provokes pain [19].

In conjunction with tissue damage growth factors are produced which are taken up and transported to the cell bodies in the dorsal root ganglia. This leads to an activation of receptors, which contributes to an increased sensitization of nociceptors and enhanced inflammation in the tissue. The result may be increased pain sensitivity and tenderness. This system warns, prevents, minimizes damage and promotes healing [25]. C- and Aδ -fibers mediate nociceptive information from both visceral and somatic sites to the spinal cord via the dorsal roots to the horn of the spinal cord where they will have a first synaptic contact with secondary neurons that are principally located in the lamina I, II and V. Second-order neurons ascend to higher centers via the contralateral spinothalamic and spinoreticular tracts. The thalamus is the key area for processing somatosensory information. From the thalamus in the brain a transmission and processing occurs in the cortex and the limbic system is responsible for the emotional-affective component of pain. The pain signals are projected to areas of the somatosensory cortex as responsible for the conscious sensory-discriminative part of the pain experience [25]. Marchand (2008) describes the interaction between pain and brain: "Pain can only be experienced when nociceptive afference reaches the cortex. Pain is a complex perception requiring central nervous system (CNS) activity" [25].

The entire process can be summarized as follows: As pain is a dynamic phenomenon, the nociceptive signal will be modulated at multiple levels of the CNS before pain is fully perceived. The modulation of the nociceptive signal starts at the periphery and involves several CNS structures, including excitatory and inhibitory mechanisms from the brainstem, the autonomic nervous system, and the cortical structures responsible for the emotional and cognitive aspects of pain perception [20, 25].

1.6 CHRONIC PAIN/PERSISTENT PAIN

Definition of chronic pain or persistent pain by IASP is pain that has lasted for three months or more, “persisted beyond the normal tissue healing time” [27]. Behind the prolonged pain are partially permanent changes, both in the neural pathways that mediate pain and in other tissues [28]. Ten to 50% of individuals develop persistent pain after acute postoperative pain in connection with common surgeries, and 2 to 10 percent of all persons with persistent pain experience the pain to be severe. On this basis Kehlet and coworkers state that persistent postsurgical pain is a major underrecognized clinical problem [23].

Several risk factors for persistent pain that have been suggested: preoperative pain for more than one month, severe postoperative pain, nerve damage during surgery, psychological anxiety and vulnerability [23, 29, 30]. Not much is known about the underlying mechanism behind persistent pain. Central sensitization and/or dysinhibition of central pain inhibitory mechanisms involving endogenous morphine are considered as the two dominant mechanisms of dysfunctional pain [31]. Reuben describes this phenomenon in a review article from 2007: It is now known that nociceptor function is dynamic and may be altered after tissue injury, which may contribute to persistent pain. Repetitive stimulation of small diameter primary afferent fibers generates a progressive increase of the action potential discharge and increased excitability of both peripheral and CNS neurons, an event termed central sensitization or "windup” [30].

Central sensitization can be developed already after a few hours of peripheral nociceptive stimulation, leading to pain prolonged beyond a duration expected after an acute event. An early hyper-excitability is often temporary if the peripheral nociception ceases. With continued or repeated peripheral nociception the risk of a permanent sensitization increases. A prolonged central sensitization has the capacity

to lead to permanent alterations in the CNS [23, 30, 31] where the end point is severe postsurgical pain, that is unresponsive to many analgesic and/or strategies [30].

Persistent postoperative pain is a well-known consequence not only after major surgeries as limb amputation, breast and thoracic surgery but also following other common types of surgery, e.g. groin hernia repair [23]. Several reports demonstrate that postoperative pain management is insufficient among 50-70% of patients undergoing different types of surgery and as mentioned before there is substantial evidence that severe postoperative pain may lead to an increased incidence of chronic pain [32, 33]. Breivik and coworkers found, in a large European interview study with more than 46.000 respondents, a prevalence rate of chronic pain between 14-40% in various countries. Nineteen percent of adult Europeans suffer from long lasting pain of moderate to severe intensity seriously affecting their daily activities and social life. Breivik states that "chronic pain is a major health problem in Europe" [34]. High age, ethnicity, education, social background, as well as depression and anxiety are associated with a high prevalence for chronic pain [25, 34-36]. The connection between unsatisfactory pain management and persistent pain is close. Kainu et al. compared persistent pain one year after CS and vaginal birth and found that it was more common with pain after CS than after vaginal birth [37]. Schytt et al. reported that more than one third of the women suffered from pain for up to two months after CS [38]. Ineffective pain management postoperatively after CS seems to increase the risk for persistent pain and correlations have been demonstrated between severe postoperative pain and persistent pain [24, 37, 39, 40]. Loos et al. reported that chronic pain was common both after hysterectomies and CS done by Pfannenstiel incision [39].

Chronic pain following CS was also described in the study by Nikolajsen and

coworkers and about one third of the patients (223 out of 690) experienced pain two years after the surgery [40].

1.7 PAIN MANAGEMENT IN HISTORY

Since ancient times, man has found different ways to treat pain and illness. Drugs used for decades are used even today, in various forms.

Herbs have always been used for medication and as painkillers. Mandragora root – mandrake, poppy seeds and juice, juice of poplar trees and the bark of the willow for example have been used as remedies [41].

Opium has been used for decades for all kinds of pain and health concerns as cough, insomnia and diarrhea. Laudanum was invented in the 17th century and is a tincture of opium and alcohol that contains almost all of the opium alkaloids. Many of the medicines were used for pain and sometimes also for cough. It was used alone or mixed with different kinds of ingredients as e.g. pearl, musk, pepper, nutmeg and saffron [42].

Laudanum was a milestone in pharmacotherapy and a very popular remedy in the 19th and 20th centuries. It was an ingredient in many patent medicines and was used for

most health issues as insomnia, bodily system failure, menstruation cramps, cold and cardiac diseases, both in adults and in children [41, 42].

1.7.1 A new era

Around 1820 the German scientist Sertürner isolated a crystalline drug out of opium that he named morphium after the Greek god of dreams, Morpheus. In 1828 the Oxford English Dictionary has the first citation in English: “morphine is the narcotic principle of opium” [43]. Morphine has been industrially produced since early-mid-1800.

Before the time of efficient pain killers skilled surgeons operated rapidly without sedative. Some doctors started to investigate how to achieve pain relief by using sedative gases, e.g. ether and chloroform [41, 44]. In 1848 a British obstetrician, James Young Simpson, proposed chloroform to be used in childbirth and surgery [41]. Analgesia during surgery was something new in the mid-1800, was revolutionary in modern medicine, but was not received entirely positive. Both in medicine and in religious circles, it was considered that pain made man strong. It was considered unethical to operate on unconscious people and it broke the law of God. A woman should give birth in pain to get the insight that she would sacrifice herself for her child [44]. John Snow invented devices for administration of ether and chloroform and the attitudes of the physicians about using chloroform during childbirth changed when he anesthetized Queen Victoria when giving birth to Prince Leopold in 1853 [41].

A new era of pain management began in 1850 when needles and syringes were invented and morphine could be injected subcutaneously (s.c). In 1898 heroin was synthesized from morphine and became a very popular remedy for “everything”, i.e. toothache, headache but most of all as cough remedy. It was said not to have as

adverse effects as morphine [41, 44]! Through successful research new opioid analgesics were developed. Semisynthetic and synthetic derivatives of morphine were developed, for example oxycodone (OXY) in 1915 and pethidine in 1939. In 1953 P. Janssen developed fentanyl, a drug that was 40 times more active than morphine, and later on came even stronger drugs, one of them sufentanil [41].

Regional nerve blocks with both alcohol and procaine were used regularly from the end of the 19th to the beginning of the 20th century. World War II opened up new opportunities to study and work with the pain of wounded soldiers. In the late 40's it was realized that pain was influenced not only by physical problems but also by emotional and cognitive factors [44].

In 1965 Melzack and Wall presented their "Gate Control Theory" dealing with the transmission of pain sensations from the periphery to the brain. This was described as the path of pain from the body to the brain being controlled by the spinal cord, which admits only a limited amount of pain impulses through different ports that are opened or closed [44].

Coca leaves or its synthesized substance cocaine was developed as a nerve block in the shift between the 19th and the 20th century. Local s.c. infiltration with cocaine as one of the ingredients was described for the first time in the beginning of the 20th century [41]. The characterization and description of the function of opioid receptors and nociception in the 1970s was another milestone in the continuing work for effective pain relief techniques. Research about administration of opioids in the subarachnoid space gave results and intrathecal (spinal and epidural) administration of opioids was used clinically from the 80's. Though morphine administration in the spinal cord was mentioned already around 1910, the improvement of local anesthetics continued throughout the 20th century with bupivacaine synthetized in the late 50's.

From the beginning of the 20th century and onwards new analgesic techniques were developed, including regional blocks and neurosurgery, to achieve pain control. A momentous event for the treatment of chronic pain was 1983 when the sustained release tablet MS Contin® (morphine sulfate) became available. In the 90's transdermal administration was found to be safe and effective both for cancer and non-cancer pain. This was later on followed by different ways to administer opioids and other substances, e.g. trans-mucosal (lollipop), intranasal or sublingual administration [41]. From the end of the 19th century, based on the knowledge of their active substances, potent and well-functioning drugs were developed. Salicylic acid was for example synthesized out of willow bark and was found to be useful in patients with rheumatism and neuralgia. Salicylic acid was developed to acetylsalicylic acid, "Aspirin", an even well-functioning synthetic drug. Starting from here the development of non-steroidal anti-inflammatory drugs (NSAIDs) continued [41]. The understanding of the entire mechanism of action behind NSAID medication was not explained until the 70's. Further research led to the next generation of pain killers. When the COX-1 and COX-2 enzymes were identified new drugs were developed without the side-effects of NSAID drugs. Patient controlled analgesia (PCA) was introduced in the 60's in obstetric patients in labor and patient controlled epidural analgesia was also developed for obstetric patients and for post-operative pain management [41].

1.8 PAIN MANAGEMENT TODAY - IN ALL SETTINGS INCLUDING MATERNITY CARE

1.8.1 Basics regarding analgesics

Bridgestock and coworkers describe the benefits of multimodal analgesia "As the transmission of pain involves many different receptors within the peripheral and central nervous system, multimodal analgesia is best employed to optimize pain control and limit side effects" [20]. A multimodal approach for analgesia uses a combination of drugs with different mechanism of action, with the aim to optimize pain management and to minimize adverse effects through additive and synergistic drug actions [17].

Pain medications, sometimes called "pain killers," usually work by targeting the receptors and neurochemical mediators. Medications can only offer a short-term relief, to eliminate the pain it is necessary to treat the underlying causes [20, 25].

1.8.2 Analgesic administration in present time

A combined approach is generally considered to be the best way to control pain [17, 45-47]. Two reviews report that a common way to achieve control of postoperative pain after CS is by systematic and/or neuraxial morphine. Morphine is mentioned as the "golden standard". The reviews conclude that the use of several analgesics of complementary mechanism of action, known as multimodal or balanced analgesia, is required to achieve a satisfactory and effective pain relief with few side effects [17, 45]. Kehlet states "with several combination regimens there is concomitant reduction of side effects owing to the lower doses of the individual drugs and differences between drugs in side effect profiles" [48]. In all settings the avoidance of adverse effects are important, but it is even more important after CS due to the need to care for and bond to the new baby and the wish to breastfeed [17, 49].

Lavoie and Toledo summarize the options for post-CS pain management [17]:

- Neuraxial analgesia (spinal, epidural and the combination spinal/epidural) with long-acting opioid.
- Systemic opioid analgesics (intravenous, intramuscular and oral opioids).
- Non-opioid analgesics (nonsteroidal anti-inflammatory drugs, paracetamol).
- Peripheral nerve blockades.
- Non-pharmacologic analgesic options (e.g. transcutaneous nerve stimulation (TNS) or massage).

1.8.3 Systemic opioid analgesics

Intravenous and s.c injections have previously been a routine way to relieve pain postoperatively. The advantages of these methods are that they are simple, inexpensive and have a long tradition in health care. The disadvantages are that it often requires repeated injections for an optimal pain relief and any delay in administration of the drug can cause frustration as the pain increases [17, 46]. Either the patient waits too long, as she doesn't want to disturb the staff [50, 51], or it takes time for the staff to respond to the patients request. Within the current tightened resources in staffing, it is usually a congested workload in the wards which can result in a delay for medical help. The time from asking for rescue medication until administration of the i.v., intramuscular or s.c. injection can be long. The time for the drug to reach the target tissue must also be included when summarizing the time until alleviation of pain [17, 46]. There is an increased risk that pain has intensified, and greater efforts are needed to control the pain. There are large inter-individual variations in the uptake of the opioids and this can lead to difficulties in finding the

correct dosing, resulting in an adequate pain relief. This may lead to an increased risk for adverse effects [46].

Many of the disadvantages associated with parenteral administration can be avoided by using patient controlled analgesia (PCA). Opioids are administered i.v. by a device and pain relief is given intermittently by demand from the patient. The positive effect is a more constant drug administration with fewer episodes of breakthrough pain which reduces the risk for persistent pain. The interindividual variability is less with continuous administration, this is important regardless of patient category. PCA may not be the optimal method for administration of analgesics in all postoperative settings. For one, it requires education of staff and patients. Another limitation with a PCA device in a maternity setting is that it might be an obstacle in the care of the baby and although it increases the autonomy in terms of pain control it also reduces the mothers' flexibility as the device has to be carried around [46]. One way to improve analgesia and to act on recommendations for multimodal treatment is to administer drugs orally. Different kinds of opioids can be given as long or short acting tablets or capsules.

1.8.4 Non opioid analgesics

NSAIDs are effective in the treatment of visceral pain, reduce the inflammatory process associated with surgery and affect the nociceptive responses associated with acute pain. Secondly, NSAIDs improve the effect of systematically or neuraxially given opioids and decrease opioid related adverse effects due to their opioid sparing effect [17, 46]. Paracetamol is often used in combination with morphine and/or NSAID medication, although different studies have failed to prove the effect of enhanced effectivity by adding this drug [17]. There have been concerns against NSAID because of potential gastrointestinal side effects and dysfunction of platelets.

The cyclooxygenase (COX-2) inhibitors are also used in post CS pain management and they may be an alternative choice as they do not inhibit platelet function [46].

1.8.5 Neuraxial analgesia

Neuraxial anesthetic techniques are common ways not only to give anesthesia during surgery but also to prevent post-cesarean pain. The function depends on two different mechanisms, the administration of the drug (epidural or spinal) and the lipid solubility of the administered drugs. Sufentanyl and fentanyl are drugs with high lipid solubility, "fast in and fast out". Morphine on the other hand is a hydrophilic opioid and has a slow onset and a longer duration of analgesia. The best way to treat post-cesarean pain with neuraxial anesthetics is using a combination of lipophilic and hydrophilic opioids. This provides a rapid onset of analgesia with long duration. There is an advantage for neuraxial administration of drugs compared to systemically given drugs as smaller amounts are needed with neuraxial administration [17, 46]. Lavoie and Toledo did a survey of 75 publications on post CS delivery pain and pain mechanisms and summarized that "in the absence of contraindications, intrathecal morphine should be considered the gold standard for providing prolonged postoperative analgesia" [17].

1.8.6 Peripheral nerve blockades

Transversus abdominis plane blockade (TAP) blockades have been put forward as efficient and complementary therapies. TAP is considered to be the most common form of peripheral nerve blockade. The blockade is done with local anesthetics into the abdominal wall. The technique is used in connection with CS but there are conflicting results on the benefits of the treatment [52-55].

1.8.7 Local anesthetics

To a great extent pain experienced after CS arises from the surgical wound. One simple way to approach the postoperative pain is to combine local anesthetic, as wound infiltration, with intravenous morphine. In the guidelines presented by The National Institute for Health and Clinical Excellence in UK (NICE) wound infiltration at CS is suggested as an efficacious alternative to other regimes [12]. Several studies support this view and in a review of 20 studies, by Bamigboye and Hofmeyr, the conclusion was that local pain management decreased the consumption of morphine postoperatively in women who had CS under spinal anesthesia [56, 57].

When proven to be efficient the use of local anesthetic as pain management would decrease the risk for opioid related side-effects as nausea, vomiting and dizziness [56, 58]. It would also decrease the risk for drugs passing over to the baby. Local infiltration of an anesthetic drug is a commonly used method in different settings [59]. Rapid onset and short acting local anesthetics e.g. lidocaine and carbocaine are often combined with adrenaline, resulting in a nearly doubled duration of anesthesia through vasoconstriction of the arteries [59]. This is due to that the resorption of the local anesthetics is delayed. Bupivacaine and ropivacaine are in contrast to lidocaine long-acting substances and in this case the function of adding adrenaline is to reduce bleeding by vasoconstriction [59].

Most common is infiltration in the surgical wound with PCA catheters [46, 56, 58, 60-62]. Givens et al. found that the morphine consumption after CS was significantly lower in a group receiving local infusion of bupivacaine in the wound than in a control group receiving saline. The catheter in the incision was left in space for 48 hours. According to the authors one weakness in this study was that the catheter itself could irritate the tissues which might lead to increased pain [61]. Fredman et al. are in

agreement with the study by Givens but they also mentioned that catheter-associated infections could be a risk and had safety concerns about pain pump failure [60].

The evidence on the benefits of a single dose of local anesthetic in the cesarean wound is limited and contradictory. Trotter et al. found that bupivacaine infiltration in the surgical site reduced the amount of rescue morphine post CS in women operated in general anesthesia, but only when the dose was adjusted for the women's weight [63].

1.9 PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics (PK) describes what the body does to the drug and pharmacodynamics (PD) what the drug does to the body.

A popular scientific way to describe PK is "A chemical cannot be a drug, no matter how active nor how specific its action, unless it is also taken appropriately into the body (absorption), distributed to the right parts of the body, metabolized in a way that does not instantly remove its activity, and eliminated in a suitable manner – a compound must get in, move about, hang around, and then get out" [64].

The acronym ADME describes the different phases the drug takes through the body. **A**bsorption of the drug by the body. The site of administration of the drug can vary and depends on the urgency and the dose of the drug affects the drug's path to action [65]. An i.v. injection is distributed directly into the venous circulation and isn't subject to first pass elimination as a drug administered orally [64, 65]. Bioavailability, dose and dosing interval control the drug concentration level in the body and hence the effect of the drug. The term bioavailability describes the amount of a given dose that enters the systemic circulation. When a drug is administered i.v. the bioavailability is 100%. If drug administration is oral (the most common way) the

compound must be absorbed in the gastrointestinal tract. The drug will pass through the liver and will to varying extent be deactivated, and in some cases activated, before entering the body circulation. Modification of the orally administered drug in the liver is called first pass effect and in general the availability of the drug taken by mouth compared to i.v. injection will be considerably less [64-66].

Many factors determine bioavailability: the route of administration, if taken together with food, interactions with other drugs, diseases, problems with internal organs, age and genetics are some of those factors. Distribution volume describes the proportion of bioavailable dose and plasma concentration of the drug. Clearance (liver- and kidney clearance) explains the body's ability to eliminate a drug and describes, for example, how much blood volume that is purified from the drug and is described in the unit ml/min. Another term is elimination half-life and it describes the time required for the concentration of the drug to reach half of its original value. It is dependent on both the volume of distribution and the clearance. C_{max} is a term that describes the peak plasma concentration of the drug after administration. T_{max} stands for time to reach C_{max} [64, 66].

Distribution through the fluids and different body tissues. Water and lipid solubility of the drug affects how the drug migrates through various biological barriers and becomes distributed in the body. Lipophilic drugs tend to be distributed into the body tissues to a greater extent than water-soluble drugs [64, 65]. Lipophilic drugs, like opioids, are easily distributed to all tissues, including nervous tissues and the brain and may also accumulate in the tissue [67].

Metabolism - recognition of a foreign substance and starting a conversion of the drug to its metabolites. A drug is often active in its primary form but in some cases the drug undergoes a metabolic activation, as in the case of activation of codeine to

morphine via CYP26D, and in some cases the drug is to varying extent deactivated already at the first step of metabolism. An active substance/metabolite will reach the therapeutic target to achieve the effect. The end point in the metabolic process is to eliminate the substance via bile or urine and in general this process involves steps converting the drug into a less lipophilic compound that is easier to excrete [67].

The metabolism or biotransformation of the drug is most often mainly proceeded in the liver but metabolism can also take place in other sites, as the kidneys, intestines, lungs and skin. The metabolism in the liver involves various enzymes and takes place through two major pathways. Phase I modification reactions include oxidation, reduction and hydrolysis, whereas phase II reactions involve conjugation with e.g. glucuronic acid or sulfate (transformation to hydrophilic substances) [64, 65]. Most opioids given orally undergo a first pass metabolism in the liver before reaching the systemic circulation, thereby decreasing the bioavailability of the drug [67].

The enzymes in the cytochrome P450 (CYP450) group are involved in the phase I oxidative reactions, involving the biotransformation of drugs as well as hormones. They have a key role in the biotransformation of drugs and are present in most tissues in the body [67, 68]. CYP2D6 alone is responsible for the metabolism and elimination of approximately 25% of all drugs and is involved in the metabolism of both codeine and OXY. CYP2C9 metabolises ibuprophen and CYP2E1 and CYP3A4 metabolise paracetamol [67].

Elimination of the substance and how it is removed from the body [64]. This elimination is dependent on metabolism as previously indicated. The liver is important for elimination and transformation of any highly lipid soluble drug to more hydrophilic metabolites and the biological function is to facilitate excretion through bile or urine. Hydrophilic drugs on the other hand primarily depend on renal function

for elimination [64]. The ability to bind different drugs differs between the various body tissues. The effect of the drug occurs when molecules attach to different receptors.

1.9.1 Opioid metabolism

1.9.1.1 Mechanisms of action

Opioid receptors are mainly located in the nervous system where the drug effect is most effective. The receptors are divided into three categories, μ (my), k (kappa) and δ (delta) receptors. The opioid receptors connected to the compounds included in this thesis are primarily μ (my) agonists as are most analgesics. They are mainly located in the CNS, brain and spinal cord as well as in the intestine.

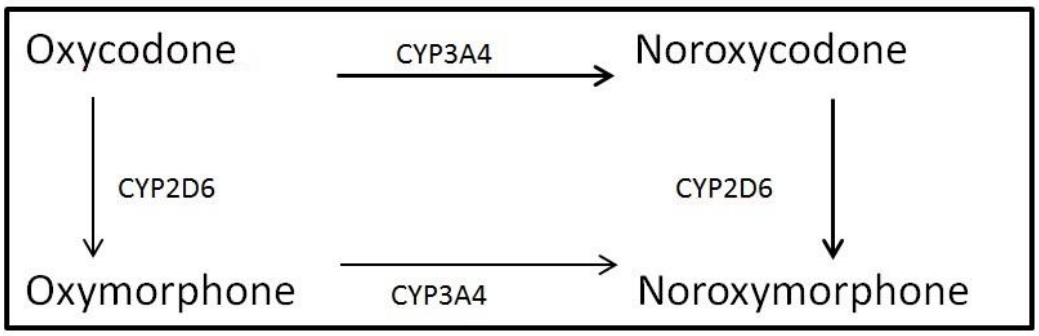
The CYP2D6 enzyme is involved in bioactivation of codeine and in hydrocodone metabolism whereas CYP3A4 is a key enzyme in the metabolism of oxycodone. Morphine is metabolized in the liver by phase 2 conjugation - glucuronidation [67]. The large variation of opioid effects can be explained by that every individual opioid has its own specific relationship to the various opioid receptors. Opioid transformation results in both active and inactive metabolites. Sometimes the active metabolite is more potent than the parent drug.

1.9.1.2 Oxycodone

Oxycodone is a lipophilic drug. The liver enzyme CYP3A4 is the main metabolizer and converts OXY to noroxycodone. CYP2D6 is also involved in the metabolism and converts a small amount of OXY to oxymorphone. The metabolic pathways for OXY are initially phase I events and the elimination of noroxycodone, oxymorphone and noroxymorphone also involves phase II metabolism via glucuronidation [69]. There is no inactive form of OXY and the active forms include oxymorphone and

noroxycodone [67, 69]. The opioid effect is mainly mediated by the parent drug OXY and it is questionable whether oxymorphone has any significant effect in pain relief [67]. Klimas recently reported that OXY itself is responsible for the analgesic effect and even if oxymorphone and noroxymorphone have a higher affinity to μ-receptors the concentration of the metabolites is low [70].

A major difference between oral OXY and morphine is the oral bioavailability, for OXY more than 60% [69].



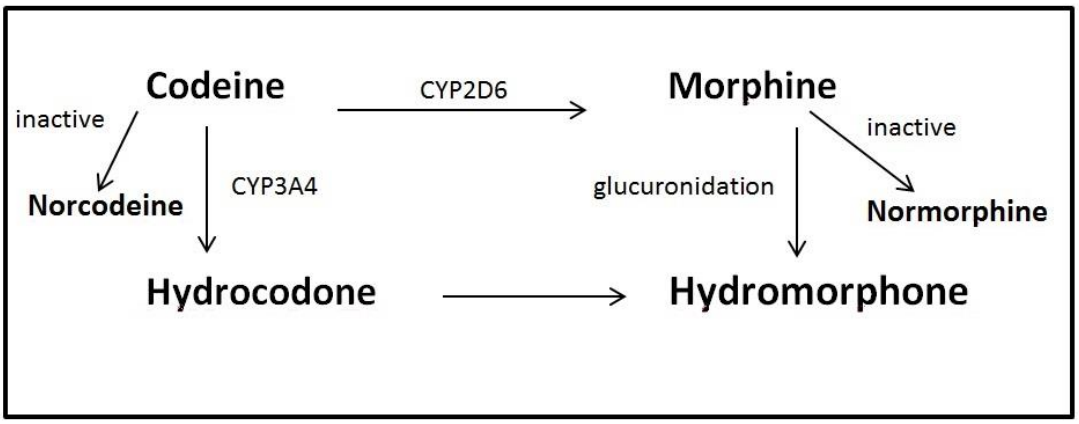
1.9.1.3 Morphine

Morphine is a lipophilic drug. The metabolic pathway for morphine is a phase II event and glucuronidation yields 2 metabolites with different efficacy, the inactive metabolite normorphine and the active metabolite hydromorphone. The mean oral bioavailability for morphine is round 30% but varies between 10 and 50% [67].

1.9.1.4 Codeine

Codeine is a prodrug that after CYP2D6 mediated activation is converted to morphine. Codeine's inactive form is norcodeine and the active form is hydrocodone. The activity of the CYP2D6 enzyme is genetically determined which can lead to an

unpredictable bioavailability of codeine [67].



1.9.1.5 Genetic factors

Genetic factors determine the activity of CYP2D6 and toxicity has been reported in CYP2D6 ultra-rapid metabolizers as they convert codeine to large amounts of morphine, whereas slow metabolizers are unable to form the active metabolite [67]. Most women have a "normal" CYP2D6 activity ("rapid metabolizers") but approximately 5% of Swedish-born women (approx. 5-10% of Caucasians) convert virtually no codeine to morphine as they possess a defect allelic variant of the CYP2D6 gene, leading to non-existent effects on pain [67, 68]. One percent of the Swedish-born population (1-7% of Caucasians) carries the duplicated or multiduplicated CYP2D6 allele, associated with very high conversion ability that can lead to toxicity and side effects [68, 71]. In some populations, such as women from Ethiopia and Eritrea, the proportion of ultra-rapid metabolizers is as high as 29% [67, 68, 72].

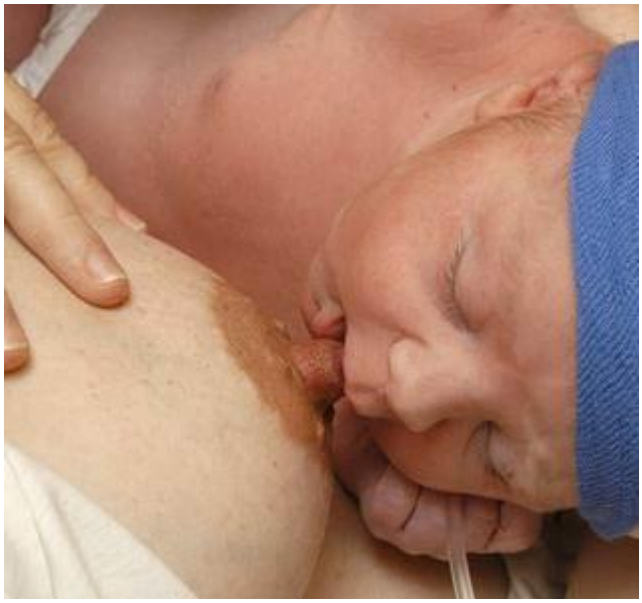
1.10 INTERACTION BETWEEN MOTHER AND CHILD IN CONNECTION WITH CESAREAN SECTION

There is a difference when taking care of a newborn child after a vaginal delivery compared to after a CS. In the latter case, the woman has not only become a mother but also needs to recover from a major abdominal surgery. Moreover, if it has been an emergency CS, in general anesthesia, the woman wakes up without knowing what has happened to her and to her baby. This may enhance the risk for fear and anxiety, increasing the already existing postoperative pain [46]. Therefore it is of paramount importance to optimize post-cesarean pain management to avoid disturbed bonding and interaction between mother and child [46, 49, 57, 73, 74].

Skin-to-skin (SSC) contact is important, the key message in the review by Stevens and coworkers says “skin-to-skin contact may reduce maternal pain, improve parent/newborn contact and communication, and keep the mother and newborn physiologically stable” [75]. Some studies also demonstrate that SSC may reduce postoperative pain [76, 77].

This assumes that all is well with mother and newborn. If the baby for some reason ends up in the NICU it is even more important with effective pain management to give the mother possibility to visit and stay with her newborn baby. It is therefore of importance that the pain relief is not only efficient but also easy to administer, not restricting the mother's ability to move [46].

1.11 BREASTFEEDING AND CESAREAN SECTION



Several studies have shown that initiation of breastfeeding and the breast milk transfer (BMT) [78] often is delayed after CS and more breastfeeding problems occur after CS when compared with vaginal delivery [75, 79, 80]. Zanardo (2010) reported that there was a delayed first breastfeeding and a lower rate of breastfeeding up to six months associated with CS. There was also a lower prevalence of breastfeeding in the delivery room after CS compared with vaginal birth. No difference in breastfeeding rates was observed between elective and emergency CS [81]. Evans and coworkers found that BMT to the baby was delayed after CS compared to vaginal birth but the difference was no longer present six days after birth. The babies' milk intake was estimated to be 4 ml/kg b.w. on day one, increasing to 44 ml/kg b.w. on day 4. It took longer for the baby to regain birth weight in the CS group compared to the vaginal birth group, at day six 40% in the vaginal birth group had regained birth weight compared to 20% in CS group [78].

It has also been reported that duration of breastfeeding is shorter after CS compared with vaginal birth [82]. Mothers delivering their babies with CS had a more stressful

attitude to breastfeeding compared to women with vaginal births. When they were asked at three and nine months postpartum the CS group reported more complicated breastfeeding than women in the vaginal birth group [83].

1.11.1 Drugs and breastfeeding

It is important with safe and effective pain relief post CS as the analgesic passes over to the baby when the drug is excreted through breast milk. Approximately 90% of all women giving birth have been shown to take some kind of drugs during the first week postpartum [84].

Ito and Lee describe the mechanism of drug transfer into milk [84]. Many factors are involved in the process, such as plasma protein binding, ionization, the drug lipophilicity, molecular weight and the drug's pharmacokinetics in the mother. Generally low molecular weight and low plasma protein binding, high lipophilicity together with cationic properties facilitate increased excretion of the drug into the milk. The lower pH in breast milk than in plasma is an important factor for transfer of basic drugs to breast milk [85]. The drugs diffuse through the mammary gland

epithelia and it is clear that carrier-mediated processes are involved with excretion of several drugs into milk [84].

Milk to plasma/serum drug concentration ratio is the ratio between drug concentration in milk and maternal plasma/serum. It is a time-dependent parameter and is influenced by factors as changes in the composition of the milk and maternal pharmacokinetics. It was proposed that the ratio can be predicted from the physiochemical characteristics of those drugs that are mainly transferred into milk by passive diffusion [84]. The fact that the milk changes over time from the first milk colostrum to transitional and mature milk must also be considered and there are composition changes within a feeding from foremilk to hindmilk. This contributes to a time- and phase dependent variation of drug excretion into milk [84].

For many drugs there are lower concentrations in breastmilk than in blood and even when exclusively breastfeeding the transfer of drug to the baby corresponds to only 0.5-2.0% of the daily dose to the mother, for most drugs being a low dose doing no harm to the newborn [84]. The level of exposure depends on the milk to plasma ratio and on the rate of clearance. Drugs with a low rate of clearance are associated with a higher level of exposure of the newborn. Even if the milk to plasma ratio is high but the clearance rate of the drug is rapid the exposure of the newborn will be limited. Ito describes it as “the rate of drug clearance by the infant is more important in determining the degree of exposure than is the milk-to-plasma ratio of the drug” [86].

He also states that a safe value is characterized as transfer of drug through breast milk leading to no more than 10% of the therapeutic dose for infants (or of the therapeutic dose to adults, standardized by weight if the infant dose is unknown).

For the opiates codeine, morphine and OXY it is a well-known fact that they accumulate in breast milk. The breast milk to plasma ratio for codeine has been

reported to be 1.3-2.5:1 [87], for morphine 2.45:1 [88] and for OXY 3.2:1 [89]. Consequently there is a risk for accumulation in the nursing baby. Another aspect that can be considered is the lower capacity to metabolize opioids in the newborns. The half-life of morphine is much longer in the neonatal period than in adults, due to a low capacity for glucuronidation [90] and the elimination of OXY is impaired in the newborn due to low capacity for N-demethylation via CYP3A4, which is a major metabolic pathway [91, 92]. Furthermore, minor amounts of OXY are metabolized via CYP2D6 by O-demethylation and the fetal levels are low also of this enzyme [91].

Several reports are available regarding serious effects of opiate exposure, especially in children born to those mothers treated with codeine who are ultra-rapid metabolizers [93, 94]. Extremely high exposure to morphine has been detected in some of these children and Koren et al. reported about one fatal case with a mother taking codeine for almost two weeks and where the baby died [95]. Due to the more constant bioavailability of oral OXY than for oral morphine and because metabolism of codeine is extremely variable OXY has become an interesting alternative for women postoperatively after CS. Some reports suggest that there are risks when giving breast-feeding women OXY for a prolonged period but for short-term use no such risks have yet been identified [89, 96]. The previously mentioned low intake of milk during the first days after CS can be assumed to contribute to these observations and risk assessments [78]. Taken together, the general view is that the risks related to opiate exposure in breast fed infants are extremely low when the drugs are given only for a short period after delivery [89, 92, 96].

1.11.2 Interference and risks with ineffective pain management

Pain management is a subjective action, where the decisions very much depend on the person that administers the medication [50]. At the maternity ward the demands on the staff are complex as accurate pain assessment and individual adjustment of treatment is extremely important in this group of patients [17, 46, 47]. New mothers are reluctant to feel sleepy or to have pain that would lead to a restriction in taking care of their baby. They are also keen to protect the baby from drug effects through the breastmilk which sometimes lead to that they do not always ask for the analgesia they need. Any medication given to this group of patients should be effective and, if possible, free from side-effects as it also interferes with a second part, the newborn baby [73, 97]. Effective pain management is an important issue after surgical interventions. The association between early mobilization, decreased risk for complications and patient satisfaction with good pain management is strong [46, 98].

Karlström and coworkers described that 78% of the women in their study scored 4 or more on the NRS scale 24 hours after the surgery. They also reported that unexpected pain was an important factor for a negative birth experience [49]. Carvalho et al. asked women what they expected before the CS and their biggest concern and fear was pain during and after the surgery, followed by nausea and vomiting [97]. There are many reasons for ineffective pain management. The patients want to be brave, they fear for addiction [46, 99] and they fear that the medication will pass over to the baby through the breast milk [97]. Another reason for ineffective pain management is that the nurses tend to underestimate the pain of the patient [100-102]. Ineffective pain management will also be a hinder for early mobilization and discharge from hospital. One third of the women in the study by Karlström et al. believed that their ability to breastfeed was affected negatively by postoperative pain [49].

1.12 CLINICAL TRIALS

The definition of a clinical trial by the Swedish Medical Product Agency (MPA) is a study that aims to discover or verify the clinical, pharmacological or pharmacodynamic effects of a drug. The trial could also identify any adverse effects, study absorption, distribution, metabolism and elimination of the drug, aiming to collect information about safety and efficiency of the drug. The MPA has a regulatory framework with guidelines about clinical trials, LVFS 2011:19. The main regulatory framework with regard to clinical research is the Helsinki Declaration. The declaration includes information about informed consent, which is of paramount importance. This means that the patient has signed that he/she is aware of the potential risks in research and has been informed about study plan e.g. that patients are randomly allocated to treatment or placebo [103, 104].

A placebo treatment means that the patient receives an inactive drug or a dummy treatment. Research has clarified that patients receiving placebo may "respond" to the drug or the treatment, a so-called placebo effect.

The idea of a clinical trial is to compare a control group (no treatment) with an intervention group that gets treatment. Most often clinical trials are performed as randomized controlled trials (RCT). RCT studies are the golden standard when it comes to compare treatment modalities [103-105]. A randomized study means that participants are randomly allocated to different groups. The procedure is considered to strengthen the study as chance determines who gets active treatment and who gets placebo. This means less risk of system errors - bias. To further reduce the risk of system failure a blinded study can be performed [103, 104].

A clinical trial is divided into different phases. Phase I is when a drug is given for the first time to a person. Phase II is normally when a drug is given to a larger group of patients suffering from a disease to study how effective the drug is to treat the

disease. Phase III is performed on a very large group of patients to conclusively define the usefulness of the drug to treat a specific disease. When Phase IIIb is performed, the drug is available in the market but new areas of use of the drug are tested (in the phase IIIa stage the drug is not yet out on the open market) [103, 104]. Study 4 in this thesis was an efficacy study and the definition is: to investigate if A is significantly better than placebo or if A is significantly better than B. In the present case OXY was compared to IVM/codeine (A versus B).

Study 1 was a double blind study, meaning that neither the patients nor the attending staff had knowledge about which treatment the patient received. Study 4 was a randomized study in which women were randomly assigned to different forms of treatment, but where both patients and staff were informed about the protocol used.

2 AIMS

The overall aim of this thesis was to investigate additional methods to improve the pain therapy in women undergoing cesarean section.

The specific aims of the papers included in the thesis were:

1. To study whether opioid consumption and pain would decrease after a single injection of bupivacaine with adrenaline close to the fascia in patients undergoing caesarean section in spinal anesthesia (Paper I).

2. To investigate the overall incidence and risk factors for persistent pain following caesarean section and to characterize the persistent pain, regarding intensity, body location and impact on daily life (Paper II).

3. To study whether a single dose of 20 or 40 ml bupivacaine with adrenaline close to the fascia would significantly influence the amount of opioids needed to achieve sufficient pain control after caesarean section in general anesthesia (Paper III).

4. To investigate if oral oxycodone can provide equal/better and safe postoperative pain relief after caesarean section compared to i.v. morphine followed by oral codeine (Paper IV).

5. To study the pharmacokinetic aspects of postoperative oxycodone treatment of mothers after caesarean section and to investigate possible drug exposure through breast milk, including the effects on the newborn (Paper V).

3 PARTICIPANTS AND METHODS

3.1 PAPER 1

Design, setting and participants

Study I was a randomized double blind controlled study. Two-hundred and sixty healthy Swedish-speaking women out of 684 consecutive patients scheduled for CS were screened for eligibility and were recruited at the Karolinska University Hospital, Huddinge. The inclusion period was between September 1st, 2006 and April 30th, 2008. Women who met the inclusion criteria (healthy women, 18-50 years old, having a planned CS from 38 completed weeks of gestation) were included. Exclusion criteria were ongoing treatment for chronic pain, history of narcotic abuse, severe psychiatric history and any intolerance against opioids, local anesthetics or other analgesic drugs given in the study. The women had to understand and speak the Swedish language. Women were recruited when they visited the clinic for a preoperative appointment the day before the CS and they were allocated into one of two groups. They gave their verbal and written consent to participate at that time.

Data collection and methods

Medical data including demographic data was collected from the computer based patient record system Obstetrix™. Pharmaceutical records were secured from the computer based patient chart system Take Care™. Primary outcome was morphine consumption and secondary variables were pain intensity assessed by NRS and mobilization parameters. A blinded local injection of study drug, 40 ml of bupivacaine (2.5 mg/ml) with adrenaline (5 µg/ml) (Marcain®adrenalin) or 40 ml saline solution (0.9%), was administered at the end of surgery before closure of the wound by the obstetrician in charge. The injection was located close to and immediately above the fascia in the subcutaneous fat. All women had spinal

anesthesia and they all got paracetamol, (1g) Perfalgan®, as a single i.v. dose after the delivery of the baby and thereafter oral administration, 1g every 6th hour, Alvedon®, combined with i.v. rescue morphine 1.0 mg/ml Morfin MEDA®, until NRS estimation was at/or below 3 for the first 24 hours after the operation. Thereafter morphine was substituted by oral codeine, Kodein Recip®, 75 mg every 6th hour. Oral ibuprofen 400 mg, Brufen®, was given as a first dose six hours after the operation and thereafter 200 mg every sixth hour. Pain assessments were performed when doing uterus palpations, at rest and when asking for rescue medication. Mobilization parameters were recorded when women were standing next to the bed, walking around in the room and when discharged from hospital. Information about surgical site infections (SSI) was also collected.

Statistical methods

The Mann-Whitney U test was used to analyze demographic data and two tailed Student's *t*-test to analyze morphine consumption and pain assessment by NRS.
A power of 80% yields, with a Bonferroni correction for multiplicity, gave a sample size estimate of 115 patients per treatment group. To compensate for withdrawals, 130 patients per arm were recruited. The level of $p \leq 0.05$ was considered significant.

Ethical considerations

The study protocol was approved by the Regional Ethics Committee in Stockholm, Sweden (2006/628-31/1), and the Swedish Medical Products Agency, (151:2006/30029). All participants gave their verbal and written informed consent to participate in the study. All study records were made anonymous by codification. No obvious disadvantage for the participants could be identified as everyone got at least the standard treatment. A minor drawback would be that the operation took a few minutes longer when injecting local anesthetics or saline.

3.2 PAPER 2

Design, setting and participants

A prospective long-term follow up study. Out of 260 healthy women from study I 253 remained for participation in the present study that was performed from September 1st 2006 to April 30th 2008.

Data collection and methods

Information on demographics, medical history, postoperative pain and analgesic requirements was collected through the records in study I. A questionnaire with the validated Brief Pain Inventory (BPI) [106] was posted to all women at 3, 6 and 12 months after the planned CS. A reminder letter was sent out within 3 weeks and a phone call was done 5 weeks after mailing the first questionnaire to minimize drop outs. Women were asked if they had experienced any pain the last week and if so to mark the pain location on a body map. They were also asked to describe pain intensity (maximum, minimum and average) and how pain interfered with their daily life activities by marking on a NRS. Pain intensities and pain interference with daily life were also documented by using the NRS, from 0 no problem at all to 10, very large problems.

Statistical methods

Demographic data were compared and analysed by Pearson´s Chi-Square test and two tailed Student's *t*-test. Stepwise multiple logistic regression analysis, with backward elimination of possible predictors was used to find possible factors related to long term pain at three, six and twelve months. In order to avoid confounders related to the pharmacological intervention in study 1 pain at 12-24 hours was used as baseline variable. The following covariates were used and analyzed separately: max NRS, mean NRS, number of breakthrough pain episodes, parity (0/≥1), previous CS (no/yes) and psychological indication (yes/no) for the CS. Significance was

calculated by Pearson's Chi Square test. The proportion of women with pain at 3, 6 and 12 months was compared using the Fischer's exact test. To evaluate how persistent pain influenced parameters related to quality of life, as assessed by BPI, the Spearman's rank test was used. Correction for multiplicity was performed according to Bonferroni. The level of $p \leq 0.05$ was considered significant.

Ethical considerations

Approval was obtained from the Regional Ethics Committee in Stockholm, Sweden (2006/628-31/1), and the Swedish Medical Products Agency, (151:2006/30029). All BPI questionnaires were codified with the result that all responses were anonymous.

3.3 PAPER 3

Design, setting and participants

A retrospective study based on statistics from CS performed at the Karolinska University Hospital, Huddinge. The study included the period between September 1st 2008 and June 30th 2014. The information was collected from the medical charts Obstetrix® and information from 250 undergoing CS in general anesthesia was included.

Data collection and methods

Five thousand one hundred and ninety three CS were performed at the clinic during this time period. The main inclusion criterion was to identify women undergoing CS in general anesthesia. There were several exclusion criteria, including any form of intrathecal anesthesia, any surgical procedure that could be suspected to markedly influence the pain e.g. postpartum hysterectomy, long term pain treatment before the surgery, peripartum death of the child, intolerance to drugs involved in the study or receiving drug treatment not following the standard protocol.

After eliminating all CS with some form of intrathecal anesthesia during delivery the number was reduced to 449. After applying the other exclusion criteria, medical charts from 250 women remained for further analysis. These were divided into three subgroups. There is a recommendation in the department to give local anesthetics subcutaneously at the surgical site, close to the fascia (40 ml bupivacaine-adrenaline; Marcain®adrenalin, 2.5 mg/ml+5 μg/ml). The recommendation was not always followed and some surgeons had chosen a lower dose. Seventy-eight records were from women receiving local anesthetics of either 20 or 40 ml in the surgical wound (36 and 42 women in each group). The control group consisted of 172 records from women not receiving any local anesthetics. The primary variable was opioid consumption 0-6 hours, 7-12 hours and accumulated 0-12 hours. No data regarding pain parameters were available but all patients got i.v. treatment with opioids as needed until NRS≤3. Demographic data, as well as information regarding perioperative antibiotic prophylaxis, SSI and duration of surgery were collected.

Statistical methods

Corrections for multiple comparisons were performed according to Bonferroni. The statistics software IBM PASW Statistics, version 18.0, was used to analyze differences between groups. Two-tailed Student's *t*-test was used for analysis of opiate consumption. For demographic data, antibiotic prophylaxis and SSI the Pearson's Chi-Square test was used. A power estimation was made based on results from study 1. This estimation suggested that to reach a power of 90% at a significance level of $P<0.05$ we would need 50 women receiving 40 ml bupivacaine-adrenaline and 50 women not receiving any treatment. As we were not able to recruit so many women to the 40 ml group the protocol was modified, i.e. we decided to recruit all the eligible patients during the chosen period. In an effort to evaluate

whether there was a dose-response relationship we also decided to collect information about the group receiving half the amount of bupivacaine-adrenaline.

Ethical considerations

The study protocol was approved by the Regional Ethics Committee in Stockholm (2012/2225-31-1). All information from patient medical records was codified to ensure anonymity. As the information was collected and depersonalized the risk was minimal that the patient would consider the study to infringe on the integrity.

3.4 PAPER 4

Design, setting and participants

This was a randomized open label parallel group study. Eighty healthy women who met the inclusion criteria were recruited at the preoperative visit some days before the scheduled CS at the Karolinska University Hospital, Huddinge. The study was performed from November 1st 2010 to August 30th 2012.

Data collection and methods

Medical and demographic data were collected from the computer based patient record system Obstetrix™. Pharmaceutical records were gathered from the computer based patient chart system Take Care™. Two telephone interviews were carried out, the first one 5 days postoperatively, to collect information about analgesic intake.

Ten days postoperatively a structured follow-up telephone interview was performed. Women were asked if they still experienced pain and about the location and type of pain. They were asked when they ended drug intake or if they still required analgesics. Questions also included pain interference with daily life, general postoperative recovery, their experience of the CS and of the general care received

On the day of discharge, all women received a questionnaire regarding their pain experience. The questionnaire included questions related to satisfaction with pain management, staffs acceptance of analgesic requirement, understanding of instructions regarding their pain treatment and, if applicable, their postoperative pain compared to previous CS. At the end of the study a Midwife Global Impression (MGI) anonymous questionnaire was handed out to a majority of the midwives (n=29/40) working at the maternity ward during the study period. Midwifes' experience of the different pain management protocols for pain relief was documented.

Randomization was performed using a computer-based program. Correct medication was prepared and ordained in the patient's records. One hour preoperatively patients received 2 g oral paracetamol, Alvedon®, as a bolus dose and all women had a spinal anesthesia according to local routines. Before leaving the operating room after surgery, all patients received oral ibuprofen 400 mg, Brufen®. Throughout the rest of the hospital stay, all patients received 200 mg ibuprofen every 6th hour. Oral paraffin emulsion (30 ml) was given twice daily to diminish constipation. In the OXY group all women received 20 mg long acting OxyContin®, as a bolus dose starting immediately after surgery. Thereafter 10 mg OxyContin® was given every 12 hours for minimum 48 hours. When needed 5 mg immediate release OXY, OxyNorm®, was administrated as rescue medication, until NRS≤3. If severe breakthrough pain 1-5 mg of i.v. OXY, OxyNorm®, diluted with 9 ml saline solution was given. In addition patients in the OXY group received 1g oral paracetamol every 6th hour until discharged.

The corresponding treatment in the i.v. morphine/codeine group (IVM) was morphine, Morfin MEDA®, diluted in saline (as needed, until NRS≤3) and paracetamol given for the first 24 hours. After that morphine and paracetamol were

substituted by a combination treatment of paracetamol 500 mg plus codeine 30 mg, Citodon®, with a maximum of 8 tablets per day. The oral analgesic treatment continued, if needed after discharge, for up to 5 days postoperatively. Women in the OXY group received 6 tablets of 10 mg OxyContin®**.** In the IVM group they received Citodon®, maximum dose eight tablets per day. Both groups were recommended to continue with paracetamol/ibuprofen when opioids were no longer required. Citodon® was replaced by paracetamol in the IVM/codeine group.

Opioid consumption was recorded and converted to oral OXY equivalents. Pain was assessed by NRS in different situations and mobilization parameters were also recorded. Several safety parameters were collected, including testing of the newborns with the Neurological and Adaptive Capacity Score (NACS) method to be able to evaluate possible effects of maternal opioid intake. Blood samples from mother and newborn as well as breastmilk from the mother were collected and analysed. Side effects in the mothers and SSI, if any, were recorded.



Statistical methods

Two-tailed Student's *t*-test was used when comparing NRS, opioid consumption and safety variables. For demographic data, interviews and questionnaires the Pearson's Chi-Square test was used. The level of $p \leq 0.05$ was considered significant.

Ethical considerations

The study was approved by the Regional Ethics Committee in Stockholm, Sweden (2010/1062-31/1) and the Swedish Medical Products Agency (151:2010/42559). All participants gave their verbal and written informed consent to participate in the study. All study records were made anonymous by codification. Swedish experience of giving OXY for postoperative pain after CS is limited but internationally there is considerable experience of OXY treatment. All mothers and children, couples in the study were monitored carefully, giving an increased security.

3.5 PAPER 5

Design and subjects

The study was designed as a descriptive post-hoc analysis of pharmacokinetic data and evaluation of safety. Blood samples and breastmilk samples included in the study originated from the OXY treatment group in the randomized trial reported in paper 4. Thirty-eight mother-neonate pairs were included in the study. Out of these, evaluable PK samples were available in 36 pairs, which constituted the population included in the pharmacokinetic analysis. The safety evaluation was based on the 38 mothers and their neonates.

Data collection and methods

Maternal blood was sampled at 24 and 48 h, neonatal blood at 48 h and breast milk was collected at 24 and 48 h, all analyzed for OXY and the metabolites noroxycodone, oxymorphone and noroxymorphone using liquid chromatography–mass spectrometry (LC-MS). Opioid consumption, maternal postoperative pain and neonatal adverse effects were observed. Any possible adverse effect of opioids on the newborns was evaluated using the NACS score at birth and at 24 and 48 h. The assessment is based on 20 criteria in five general areas: adaptive capacity, active and

passive tone, primary reflexes and general observations (motor activity, alertness and crying). Each item is scored as 0, 1 or 2, adding up to a maximal total score of 40. Scores ≥35 indicates a healthy newborn.

Statistical methods

The neonate safety variables including NACS, weight development and any aberrant observations regarding the newborns were analysed. descriptive analyses and absolute changes from baseline were used. The square of the Pearson product-moment correlation coefficient (R^2) was used to quantify the relationship between plasma and breast milk concentrations for oxycodone and its metabolites.

Ethical considerations

The study was approved by the Regional Ethics Committee in Stockholm, Sweden (2010/1062-31/1), and the Swedish Medical Products Agency (151:2010/42559).

4 RESULTS

4.1 PAPER 1

Morphine requirements were significantly less in the bupivacaine group for up to 12 h. In the immediate postoperative period, 0-6 h, there were lower mean and maximum pain scores by NRS, between the bupivacaine and control groups ($p \leq 0.001$). When analyzing the number of requests for rescue opioids during the first six hours, 47 women in the control group needed five injections or more, compared to 21 women in the bupivacaine group. Thirteen women in the bupivacaine group compared to three in the placebo group never asked for any rescue morphine at all during the first six hours postoperatively. This difference in demand for rescue medication between bupivacaine and placebo was significant.

There were no differences between the two groups in time for mobilization or discharge from hospital. Two hundred and fifty three (bupivacaine n=128/control n=125) women responded to the telephone interview, performed ten days after surgery. According to the interview, 128 women expressed that pain relief was as they expected and a total of 103 women expressed that pain relief had been quicker than expected. The majority of women, 167 stated that the pain was no obstacle in their daily life 10 days after the CS. No difference was observed between groups at this time point.

4.2 PAPER 2

The response rate was high with 91% (231/253) at 3 months, 90% (228/253) at 6 months and 85% (215/253) answers one year after the CS. At 3 months 56% (52/93) of all responders with pain reported pain in and around the surgical site and 32% (30/93) of those with pain reported pain on several locations. At 6 months 25% (20/63) of the responders with pain reported pain at more than one location on the

body map. At that time point 59% (37/63) of the responders with pain marked on the body map the pain to be around the surgical site and the corresponding proportion at 12 months was 26% (12/46). The total number of women with pain localized to the abdomen decreased over time from 52 (3 months), to 37 (6 months) and finally to 12 women (12 months). The percentage of women reporting pain at any body location at all 3 time points were 40% (93/231) 3 months, 27% (63/228) 6 months and 21% (46/215) 12 months.

Fourteen women reported abdominal pain at both 3 and 6 months whereas 6 women had pain at this location at all 3 time points. Risk factors for persistent pain were calculated by multiple logistic regression analysis. The result showed that having a first time CS led to a significantly higher risk for persistent pain at 3 and 6 months following CS. Surgery performed with psychological indication (maternal request) increased the risk for pain at 3 months. Severe postoperative pain or first time CS were significant independent risk factors for developing chronic pain for up to 6 months postoperatively. The most common indications for elective CS were psychological/maternal request (36.5%) followed by previous CS (18.1%), breech presentation (17.7%) and previous sphincter/perineal rupture (13.1%).

In the BPI questionnaire we found that parameters related to quality of life were impaired in women with persistent pain. There was a significant correlation (Spearmans's rank test) between pain intensity and interference with all seven functional domains related to function and quality of life at 3, 6 and 12 months.

One fourth of all women with pain had sleep problems at 3 months. It would have been interesting to know how the frequency of sleep problems would have been if all women, even those without pain, had been asked. Quite a few women (22%) reported that pain, at all three time points, had an impact on the variable enjoyment of life. There was an open ended question in the BPI questionnaire. Many of the responders

used this as an opportunity to write free comments. Most of the answers were about scar pain and/or sensations. At 3 months about 46% (107/231) of all the responders used the possibility to make free comments and 13 of the comments regarding scar sensations (n=36) were from women with no reported pain. Furthermore, all women responding to the open question reported that the scar itched, was numb and/or hypersensitive, that clothes worn over the scar were irritating or that they experienced a total lack of sensation in the skin around the surgical site. At 6 months 34% (77/228) of the responders wrote free comments. Scar sensation (n=25) was still the most frequent topic, followed by mobility (n=19) and pain (n=19). Twelve months after the CS, 30% (65/215) of the responders used the free comments. Remarks about pain (n=21) followed by comments about mobility (n=15) and scar sensations (n=10) were most frequent Fig. 1. At 12 months the questionnaire was also spontaneously used by the responders' to "close the study and the CS", i.e. as a summary. There were 23 comments about wellbeing, satisfaction with the CS and/or with treatment in the maternity ward.

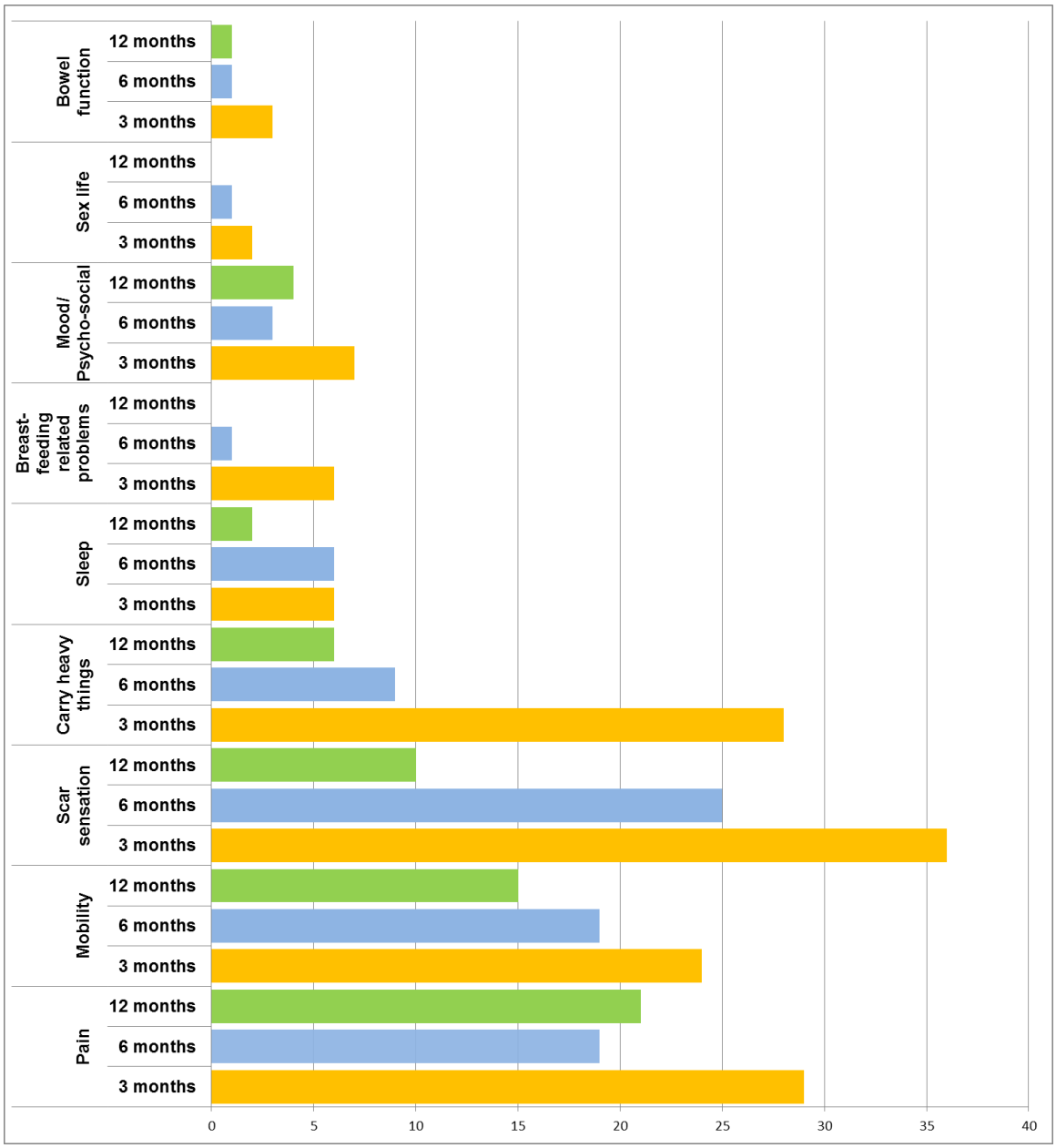


Figure 1. Free comments from women in the different time points were categorized into 9 different categories.

4.3 PAPER 3

There was a significant lower BMI in the group receiving 20 ml bupivacaine than in the two groups, otherwise there were no other differences regarding demographics.

A significantly lower opioid consumption was found during the first 0-6 h following CS in women receiving 40 ml bupivacaine-adrenaline in the surgical site when compared with controls ($p \leq 0.05$). No such difference was seen with the 20 ml group.

There were no significant differences between the two "treatment groups" found at any of the periods analyzed. The most common indication for emergency CS at our department was fetal distress. Nearly 93% of those who should have prophylactic antibiotic treatment according to the routine protocol got it. Surgical site infections were rare with a total of 7, all groups included and all of them had received prophylactic antibiotic treatment. No significant difference in SSI was seen when controls were compared with all patients receiving local anesthetics.

4.4 PAPER 4

Eighty women were recruited (40+40). Two women in the OXY group and one woman in the control group had to be excluded. There was significantly lower pain intensity when asking for rescue medication in the OXY group than in the IVM/codeine group the first 24 h following CS. Provoked pain (uterus palpation) 0-6 h was also less in the OXY group.

There were, however, no differences between the groups when looking at opioid consumption or mean pain intensity at rest (0-24 h). Both pain intensity and opioid consumption were lower in the OXY group 25-48 h post CS. It took significantly less time to administered OXY than IVM/codeine. We found no serious adverse effects among women in any of the groups although the number of common opioid adverse effects was higher with IVM/codeine. No adverse outcomes in the newborns related to treatment were observed in either group.

When answering the questionnaire on the day of discharge most women (76/80) experienced adequate pain alleviation and were satisfied with pain management. Ten women (four in the OXY group and six in the IVM/codeine group) reported unsatisfactory pain relief. Despite this, all women told that they gained support for their reported need to relieve the pain and they understood instructions about pain treatment. On postoperative day 10 analgesics requirements were low and similar between groups. Women in the OXY group experienced a greater well-being than in the IVM/codeine group (100% vs. 87%; not significant) and reported pain as less of an obstacle than in the IVM/codeine group (79% vs. 51%; p=0.011). The care in connection with the CS and at the maternity ward was perceived as positive or very positive. All midwifes (n=49) receiving the MGI questionnaire responded. Most of them judged the OXY group patients to have less pain (93.1%; 6.9% considered treatments equal) and that the women were easier to mobilize (88.9%; 11.1% thought it was the same). A majority of the staff (79.3%) judged patient contentment with analgesic treatment to be better in the OXY group while 20.7% considered protocols equal. A majority perceived workload to be less with OXY treatment while others judged it as similar (72.4% *vs* 27.6%). Most midwifes (93.1%) apprehended oral drug administration (OXY) as less time consuming than i.v. injections (IVM), which was confirmed by the time study.

4.5 PAPER 5

All 36 mothers with plasma samples had detectable OXY levels and achieved adequate pain relief. Thirty-three mothers had quantifiable levels of noroxycodone and noroxymorphone. Only one mother had a quantifiable oxymorphone concentration in the plasma.

Several milk samples were excluded due to small amounts or other reasons associated with laboratory analysis. Breastmilk samples at 24 hours could be analysed in 14 mothers. Thirteen women had quantifiable OXY levels, in 12 noroxycodone could be detected and in 10 women noroxymorphone was found. No woman had a quantifiable level of oxymorphone.

At 24 hours postoperatively 11 mothers had quantifiable levels of OXY and noroxycodone in both plasma and breastmilk. When analyzing noroxymorphone 8 mothers had quantifiable levels in both plasma and breast milk.

At 48 hours quantifiable levels of OXY were observed in plasma and breastmilk from 18 mothers. Fourteen mothers had measurable levels of noroxycodone in both plasma and breast milk and there were 10 mothers who had quantifiable levels of noroxymorphone in plasma and breast milk.

Blood samples from 36 newborns were collected but only four had quantifiable OXY concentrations. In 16 children no oxycodone could be detected at 48 hours. Eleven samples could not be analysed due to technical difficulties. One sample had an inferring peak and the remaining four children had oxycodone levels below the limit of quantification. In the four neonates with detectable plasma concentrations of OXY, NACS scores at 0, 24 and 48 hours were within the normal ranges. One neonate had a high oxycodone plasma level of 232, a result the accuracy of which was questioned as the NACS scores indicated a normal status. Several factors indicate the incorrectness in the value as it would involve large amounts of breast milk, and a large drug intake in the mother, which was not present in this case. This result may be questioned and the likely explanation is an erroneous result in the chemical analysis.

One neonate developed a pulmonary adaptation disturbance (PAS) at 24 hours detected by the NACS and the baby was transferred to the NICU. This neonate had no detectable OXY plasma concentration.

5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

The first study in this thesis started, in the beginning of September 2006 and the last one ended in August 31th 2014, which means 8 years of data collection.

Studies included in the thesis mainly constitute a quantitative approach but in some cases qualitative methods are involved. Statistical calculations were used to analyze the quantifiable results such as morphine consumption, mobilization and pain parameters. The qualitative data was collected through interviews and open-ended questions in the questionnaire and the material was then analyzed.

To investigate the differences between the groups in study 1 and 4 a randomization was performed. A strength of the studies included in this thesis is the large number of participants and the high response rate. However, a limitation was identified in study 5 since many samples could not be analyzed due to problems in the laboratory. Nevertheless, the results of the latter study are still important because it adds new information to studies previously published.

There was few data missing and a low number of withdrawals in all studies. The protocols for pain treatment and the study protocols were rigorously followed by the staff. The high compliance may be due to a small group of investigators working closely together with the ward staff. Daily monitoring and interested coworkers are also central for reliability and high quality of study results.

In study 2 there was a lack of information about pre-operative pain and other factors e.g. genetics and preexisting anxiety or other psychological aspects that would have been interesting to investigate. A strength of study 2 compared to other publications regarding long-term follow-up was that it minimized the recall bias as the women did

not have to recall the postoperative pain. The first set of data was collected in close connection to the CS.

There are limitations when conducting a register based study as in study 3 as there is no possibility to affect the background information and one has to trust the material. A strenght of the study was that few parameters were investigated and that information was collected during pregnancy and in close connection to the surgery.

A double blinded randomized study would have been the best choice for study 4 but the reason for not using this method was the ethical aspect of collecting blood samples from all the newborns as well as milk samples from the mothers. When choosing not perform a double blinded study the sampling could be limited to the OXY group, which we considered to be more important as there is less data about this opioid. There were no drop outs due to allocation to either group. In connection with routine blood sampling for PKU an extra blood sample was collected which did not result in any additional pain to the child.

Another limitation to this study was that we never did any CYP2D6 pharmacogenomics analyses, and therefore some women in the IVM/codeine group might have been slow metabolizers, not responding to codeine, affecting their response to treatment. NACS evaluation was found to be a valuable tool in this study and was performed only by two trained persons.

It is an ethical question to sample colostrum from new mothers for pharmacokinetic analysis, although all mothers accepted. The benefits of the knowledge about how OXY works in lactating mothers was considered greater than eventual disadvantages. One major challenge in this study was the small samples of breastmilk in the first 24 h as some breast milk samples had to be diluted before analysis. This has contributed to some uncertainty regarding interpretation of the results. There were

also some problems with samples that could not be evaluated due to technical problems with the chemical analysis.

5.2 DISCUSSION OF THE RESULTS

The frequency of CS increases globally and care around CS is a dynamic process as surgical methods and anesthetics change and improve over time. Studies included in this thesis extend over a number of years and much has happened in the pain management field during this period. Studies included in the present thesis has investigated pain associated with CS from different perspectives, investigated several forms of pain management methods related to the CS and evaluated in what way pain affects women in both the short and the long term. There are high demands on the staff as it is important to offer methods for pain relief that as little as possible affects the newborn through the breast milk. The new mother also needs to be confident about the protocol and not refrain from accepting analgesia due to fear that it will affect the baby. It is necessary to identify various efficient CS pain management methods that can be used in different settings, both in low income and high income countries. It is important that all women undergoing a CS should have the best possible chance for a good start with the newborn. This means that no matter where women live in the world they should have access to an efficient pain treatment following CS.

In general multimodal analgesia is the best way to relieve pain postoperatively. This is even more relevant when it comes to CS as the pain is a combination of visceral pain due to uterus contractions and nociceptive pain due to surgery. Both oral administration of opiates and local anesthesia represent ways to improve pain management.

In study 1 and 3 the results showed that local anesthetic in the surgical site decreased postoperative opioid consumption and was an easy way to improve pain control. Some studies have been performed investigating local injection of anesthetics in connection with CS and the review by Bamigboye and Hofmeyr's [57] as well as a study by Ranta and coworker [56] confirm the findings in study 1 and 3. Studies have shown [23, 29, 30] that worry and anxiety aggravates the pain. After CS in general anesthesia women often wakes up without any form of pain relief. Concerns about the situation and unawareness of what has happened to her and to her child can affect the pain negatively. The greatest benefit for local analgesia is that it can be initiated before ending the general anesthesia, which can improve postoperative pain control. The new mother should not have to deal with both maximum pain and anxiety at the same time. According to study 1 local anesthetic in the surgical wound contributes to analgesia for at least 6 hours postoperatively and there is time for additional pain treatment to be initiated. Local anesthesia is an easy procedure and is a simple alternative to more invasive methods.

Study 4 was conducted to evaluate if oral administration of a potent opioid would be beneficial after CS compared to i.v. morphine followed by oral codeine. Several studies during the last years have reported about adverse effects and even death in newborns where the mothers were on codeine medication while nursing [93-95]. Due to differences in codeine metabolism the bioavailability is difficult to predict. This was the main reason to investigate and consider the option to phase out codeine from the standard medication at clinic at Karolinska University Hospital. The choice of oral OXY instead of oral morphine was motivated by its good and less variable bioavailability (19-47% *vs* 67-80%), further reducing the interindividual variability [69, 107].

The comparison between intake of parenteral morphine and oral OXY was in general favorable for latter. Several different parameters were analyzed related to the safety of the mother and her newborn. The present study did not identify any safety risks in any of the groups when women were treated for only a short period after CS. However, to be conclusive concerning safety a study would have had to include many more patients but our results add valuable information to previous studies and the accumulating clinical experience of using OXY. Take together we suggest that OXY is an excellent choice of opioid when compared with the previously used schedule, especially as the oral administration worked very well.

Another experience from the study was that the NACS assessment turned out to be a useful tool to evaluate the newborns. On a number of occasions morbidity, like e.g. PAS in the baby was early identified and it is reasonable to assume that diagnosis otherwise would have been delayed. Above all, it was the parts of the NACS assessment concerning active and passive tone that in the current setting turned out to be most effective in finding babies at risk.

Study 5 fills a gap in the current knowledge about how OXY and its metabolites are excreted in serum and milk and how it passes over to the baby. An additional strength of this study is that the possible impact of OXY on the baby has been studied and verified by NACS scores and other safety variables. The purpose of the study was similar to a study by Seaton and coworkers [89]. However, in the previous report only the parent compound OXY was investigated and less data on the potential impact on the newborns was presented. It is important to explain to the newly delivered mother that early after CS only small amounts of OXY passes over to the baby through breast milk. Drug levels in blood and breast milk are usually at most the first 24 h but BMT has been shown to be delayed following CS. Furthermore, milk production is low and in fact very small amounts of the drug are passing over.

It appears clear that an effective pain relief reduces the risk for chronic pain after CS. Study 2, confirmed already existent evidence [24, 37, 39, 40] that severe postoperative pain is associated with chronic pain. However, no other studies have been found reporting that psychological indication, maternal request, as well as having a first CS would increase the risk of pain. When conducting study 2 the hypotheses was that numerous CS would enhance the risk of pain because of the increased risk of adhesions, which could not be confirmed in the study. To make women aware of the importance of sufficient pain relief it could be valuable to consider informing about risk factors for long term pain before the CS, thereby increasing their motivation to demand the best possible pain control. It could also be reasonable to inform women about these risk factors when they ask for a CS without any strictly medical reason.

Today, most women have a spinal anesthesia with the addition of morphine at CS. This has been shown to provide an exceptionally good pain relief also postoperatively, with minimal need for intravenous or oral opioids. For women undergoing caesarean section under general anesthesia, there is still a pronounced need for multimodal treatment. The strategies we have studied, local anesthesia in the surgical wound and oral treatment with OXY, can improve pain relief in these women.

6 CONCLUSIONS AND FURTHER DIRECTIONS

- Local anesthetic in the surgical wound is an easy and efficient tool for pain management. It is opioid-saving and will contribute to pain control in the immediate postoperative period where other strategies for pain relief can be initiated.

- Since intrathecal anesthesia including morphine now has become the golden standard for pain relief at CS it can be assumed that the greatest benefit of local anesthesia would be apparent when the operation is performed in general anesthesia.

- Severe postoperative pain increases the risk for persistent pain after CS. Increased risk for long term pain was also present at a first time CS, and if the indication for CS was maternal request.

- It is an open question how women should be informed about the risk of persistent pain after CS. One reason to inform about the risk would be to point out that women always should ask for adequate pain medication and thereby possibly reducing this risk. It is also reasonable to inform women when asking for CS without any medical reasons (maternal request) about the long term consequences.

- The result shows that oral OXY compared to i.v. morphine and codeine was an effective and safe treatment of pain in the first days after the CS. Only minor adverse effects of opioid intake were found in the mothers and none in their babies. The amounts of OXY or its metabolites were excreted from the woman to the baby through breast milk in such small quantities that it cannot be expected to affect the child when used only for a few days after delivery.

- Constipation is a general problem when using opiates. There is another choice available today for oral opiate treatment, i.e. OXY plus naloxone (Targiniq®, Mundipharma). To our knowledge no studies regarding this drug in connection with postoperative pain control after CS has yet been published.

In the future the following aspects regarding research as well as clinical topics should be addressed:

- Prospective studies investigating not only the need for opiates but also pain and mobilization parameters after CS in general anesthesia, in connection with local anesthesia.

- To investigate if the combination of OXY and naloxone could improve postoperative treatment after CS by diminishing the problems with constipation.

- To perform prospective studies aiming to investigate severe postoperative pain and the risk for persistent pain, including how preoperative pain can influence the process.

- T inform both care givers and women facing a CS about how pain assessment and pain relief works, why it is so important both in the short and long term perspective, to be pain relieved and guide women about when to ask for medication.

- The new mother should also be informed that most drugs used in connection with delivery can be taken during breastfeeding. This is important because many new mothers do not take enough medication because of concern for transmission to the baby through breast milk.

- The care givers should be continuously informed about the mechanisms behind pain how pain relief works and why it is so important to listen to and rely on the woman's description of her pain.

7 SVENSK SAMMANFATTNING

Kejsarsnittfrekvensen ökar i hela världen och på en del kliniker är hälften av alla förlossningar ett kejsarsnitt. I Sverige har siffran i flera år legat strax under 20%. Läkemedel och olika behandlingsmöjligheter förbättras hela tiden och dagens sjukvård kan erbjuda ett flertal olika alternativ. Samlade forskningsresultat talar för att ett multimodalt synsätt ger de bästa förutsättningarna för smärtbehandlingen efter ett kejsarsnitt. Det innebär att man kombinerar olika former av läkemedel och administrationssätt för att kunna behandla olika former av smärta varvid man kan undvika att ge för stora mängder av de enskilda läkemedlen. På så sätt minskar man också risken för biverkningar. När det gäller behandlingen av operationssmärta efter ett kejsarsnitt ställs det extra höga krav på läkemedel då det är olika former av smärta, dels från operationssåret och dels från livmoderns sammandragningar. Det är också viktigt att använda läkemedel som den nyblivna mamman samt vårdpersonal kan känna sig trygga med, då det inte skall påverka barnet med tanke på överföring av läkemedlet via amningen.

Det är viktigt att underlätta både amning, anknytning mellan mor och barn och mobilisering, vilket kräver en så smärtfri postoperativ period som möjligt. Det övergripande syftet med avhandlingen var att undersöka hur smärtlindringen hos kvinnor som genomgår ett kejsarsnitt kan förbättras. De fem olika studierna som ingår i avhandlingen har på olika sätt haft som syfte att belysa hur smärtan ur olika perspektiv påverkar kvinnan och hennes barn.

I arbete 1 studerades om lokalbedövning i operationssåret skulle innebära några fördelar för kvinnan. En randomiserad studie genomfördes där den ena gruppen fick lokalbedövning i operationssåret och den andra gruppen fick koksaltlösning. Resultatet visade att lokalbedövningen (bupivakain-adrenalin) minskade behovet av

morfin efter operationen och att dessa kvinnor hade mindre ont. I studie 2 följde vi kvinnorna från studie 1 vid tre olika tillfällen upp till ett år efter kejsarsnittet. Vid 3, 6 och 12 månader skickade frågeformulär ut om eventuell kvarstående smärta och hur denna smärta påverkade kvinnorna i deras dagliga liv. Kvinnorna fick också beskriva smärtans lokalisation och vilken typ av smärta det rörde sig om. Vid 3 månader hade 40% av kvinnorna ont och vid 6 och 12 månader var motsvarande siffra 27% och 21%. Många gånger hade kvinnorna ont på fler än ett ställe på kroppen och smärtan påverkade dem i deras dagliga liv. Vid 3 månader visade resultatet att både kejsarsnitt på psykologisk indikation (kvinnans begäran) och ett första kejsarsnitt ökade risken för långvarig smärta. Vid 6 månader fann vi att svår postoperativ smärta ökade risken och även här innebar ett första kejsarsnitt en riskökning med avseende på långvarig smärta.

I den tredje studien gjordes en journalgranskning på kvinnor som genomgått ett kejsarsnitt i narkos på sjukhuset sedan 2008. Syftet var att undersöka morfinförbrukningen hos de kvinnor som fått lokalbedövning (20 eller 40 ml bupivacain-adrenalin) i operationssåret i samband med kejsarsnittet jämfört med kontroller som inte fick denna behandling. Även denna studie visade att det fanns ett minskat behov av opioider hos gruppen som fått 40 ml lokalbedövning men ingen signifikant effekt hos gruppen som fått 20 ml.

I den näst sista studien, studie 4, undersöktes om oralt oxykodon (OXY) var ett säkert och lika bra eller bättre läkemedel jämfört med intravenöst (i.v.) morfin följt av oralt kodein. Alla kvinnor fick även paracetamol och ibuprofen. Opioidförbrukningen var signifikant mindre i OXY gruppen, liksom den skattade smärtan hos kvinnorna. Biverkningarna hos mödrarna, dock lindriga sådana, var signifikant fler i morfin/kodeingruppen. Tiden att administrera läkemedlen jämfördes och det gick

signifikant fortare att dela ut OXY- tabletter än att spruta i.v. morfin. Det var inga skillnader mellan grupperna när det gällde säkerhetsaspekter för barnen.

Studie 5, var en farmakokinetik studie. Serum och bröstmjölk från de kvinnor som ingick i OXY gruppen i studie 4 samt serum från deras barn analyserades med avseende på OXY och dess metaboliter (noroxycodone, oxymorphone and noroxymorphone).

Det fanns detekterbara mängder av OXY i alla kvinnors serum och hos de flesta var även noroxykodon och norxymorfon mätbara. Mätbara nivåer av OXY och dessa två metaboliter kunde i de flesta fall även identifieras i den bröstmjölk som gick att analysera. I de allra flesta fall fanns låga eller icke mätbara mängder OXY i barnens blod. Inga biverkningar eller patologiska NACS-bedömningar som kunde härledas till opioidbehandlingen av mödrarna sågs hos något av barnen.

Sammafattningsvis är lokalbedövning i operationssåret en enkel behandlingsform både vid kejsarsnitt i spinalbedövning och vid kejsarsnitt i narkos. Även oral behandling med OXY är en effektiv behandling där de aktuella studierna inte kunnat identifieras några negativa effekter hos mödrarna eller hos det nyfödda barnen.

Bägge behandlingsformerna, lokalbedövning och oralt OXY minskar opiatbehov och postoperativ smärta. En mindre mängd opioider kan förväntas minska risken för biverkningar och minskad smärta kan bidra till att minimera risken för långvarig smärta efter kejsarsnitt. De strategier som har studerats i denna avhandling, lokalbedövning i operationssåret och tablettbehandling med OXY, kan vara till god hjälp för att tillgodose behovet av postoperativ smärtlindring hos framför allt de kvinnor som genomgår kejsarsnitt i narkos.

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