From The Department of Clinical Sciences,
Danderyd hospital
Karolinska Institutet, Stockholm, Sweden

PAIN RELIEF DURING LABOUR AND FOLLOWING OBSTETRIC AND GYNAECOLOGICAL SURGERY WITH SPECIAL REFERENCE TO NEUROAXIAL MORPHINE.

Anette Hein

Karolinska Institutet

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Front page:
Papaver somniferum, commonly known as the opium poppy
Picture: Linnéa Hein

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Pain relief during labour and following obstetric and gynaecological surgery with special reference to neuroaxial morphine

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Anette Hein M.D.

Principal Supervisor:
Professor Jan G. Jakobsson
Karolinska Institutet
Department of Clinical sciences
Danderyd Hospital
Division of Anaesthesia and Intensive Care

Co-supervisor(s):
Associate Professor Caroline Haegerstrand
Karolinska Institutet
Department of Clinical sciences
Danderyd Hospital
Division of Anaesthesia and Intensive Care

Opponent:
Associate Professor Lena Nilsson
Linköping University
Department of Medical and Health Sciences (IMH)
Division of Drug Research

Examination Board:
Associate Professor Märta Segerdahl
Karolinska Institutet
Department of Physiology and Pharmacology

Professor Sigridur Kalman
Karolinska Institutet
Department of Clinical Science, Intervention and Technology (CLINTEC)

Professor Anna-Karin Wikström
Uppsala University
Department of Women's and Children's Health, Research group; Obstetric research

To Johan, Linnéa, Victor, Maria, and Elin.

”Det anstår inte den vise att ha bråttom”
Heliga Birgitta 1303-1373

ABSTRACT

Background: Pain is a major clinical problem during childbirth and postoperatively after caesarean section (CS) and hysterectomy. There are several reasons why pain should be minimized; pain is indeed a negative sensation, it affects the birth-experience and the entire post-operative recovery, with reduced wellbeing and extended time in hospital. Inadequately treated pain is a risk factor for persistent pain. Multimodal pain treatment, combining different analgesics with different mode of action to reach additive or synergistic analgesic effect; thereby gain effective pain management but a lower incident of side effects has become praxis. Adding small amounts of morphine to local anaesthetic for spinal anaesthesia is an attractive combination improving intraoperative anaesthesia and postoperative analgesia. The use of intrathecal morphine (ITM) is however associated to side effects, where respiratory depression is the most feared adverse effect, which restricted its use. Obesity per se is associated with risk for respiratory complications e.g. sleep apnoea and hypoventilation. Thus obesity, ITM and pregnancy may act additive increasing risk for respiratory depression and the risk for respiratory depression has been seen more commonly in obese mothers after caesarean section CS. The aim of this thesis was to study morphine as adjunct to bupivacaine in neuroaxial anaesthesia in different perspectives; ITM used in spinal labour analgesia, ITM used in spinal for post hysterectomy pain, the use of neuroaxial administered morphine in Sweden, the role of polygraphic registration in obese mothers after CS in spinal anaesthesia including ITM and finally the use of general and regional anaesthesia ITM in emergent CS.

Methods and Main Results: Study I and **II** are randomized double-blinded placebo-controlled trials investigating the effects of different doses of morphine added to local anaesthetic intrathecally.
In **Study I** we compared the addition of morphine 50, 100 μg or saline to intrathecal bupivacaine (1.25 mg) and sufentanil (5 μg) to evaluate the impact on duration of labour analgesia as part of a combined spinal-epidural technique in 90 nulliparous labouring women. Duration of analgesia was defined as the time from intrathecal injection to the return of pain VAS >4. No significant differences were seen in onset or duration of analgesia, obstetric and neonatal outcome or side effects, between the groups.
In **Study II** ASA I-II women (n=144) scheduled for abdominal hysterectomy in combined general and spinal anaesthesia were randomised to spinal anaesthesia with 12 mg of hyperbaric bupivacaine combined with 100, 200, and 300 μg morphine or saline. Primary outcome was 24 h used nurse administered and patient controlled analgesia (PCA)-morphine. ITM reduced accumulated 24 h post-operative morphine consumption. Morphine 100 μg reduced morphine consumption significantly vs. placebo at 0–6 h, 6–12 h, and for the entire 0–24 h after operation. Morphine 200 μg further reduced morphine consumption significantly vs. morphine 100 μg at 0–6 h and for the entire 0–24 h after operation. Morphine 300 μg did not further reduce the morphine consumption. Emesis was experienced similar in all groups, and pruritus occurred only in the morphine groups. No serious side effects were observed.
In **Study III** we investigated the use of intrathecal and epidural opioids in mainly CS, and hysterectomies in Sweden by a questionnaire to anaesthetists in charge of obstetric

anaesthesia units. We had 68% of units responding and found in CS spinal anaesthesia, 20/32 units use ITM, the most common dose was 100 μg (17/21). Addition of intrathecal fentanyl (10-20 μg) or sufentanil (2.5-10 μg), was used by 21 and 9 units respectively. In CS epidural anaesthesia 12/32 clinics used epidural morphine, the majority of units used a 2 mg dose while use of fentanyl (50-100 μg) or sufentanil (5-25 μg) was more common, in 10 and 15 units respectively. For hysterectomy ITM was used by 20/32 units (80-200 μg), the majority used 200 μg dose (9/32). Risk of respiratory depression and difficult to monitor postoperatively was the main reason for withholding intrathecal opioids in 7/12 units.
Study IV is a prospective observational study to explore the occurrence of sleep disorder breathing in obese mothers and use of portable sleep apnoea polygraphy for respiratory monitoring the first night after CS with bupivacaine/morphine/fentanyl spinal anaesthesia, assessing the occurrence of apnoea/hypopnea index (AHI) and oxygen desaturation index (ODI). Among the 20 mothers that completed polygraphic registration: 11 had normal apnoea-hypopnea index (AHI <5) 7 had mild; AHI ≥5 and <15; and 2 had moderate; AHI ≥15 (15.3 and 18.2) but no one had severe obstructive sleep apnoea, OSA (AHI ≥30). Those mothers with moderate OSA did not show high ODI or signs of hypercapnia on transcutaneous CO_2 registration. The ODI was on average 4.4, eight mothers had an ODI >5. Mean saturation was 94% (91-96%), and four mothers had mean saturation between 90-94%, but none had a mean SpO_2 <90%. None of the mothers showed clinical signs or symptoms of severe respiratory depression, registered by routine clinical monitoring.
Study V is a retrospective chart review of emergency CS (ECS) at Danderyd Hospital between January and October 2016 with the aim to assess the decision to delivery interval (DDI) and the impact of chosen anaesthetic technique, general anaesthesia (GA), spinal anaesthesia (SA) with opioid supplementation, or "top-up" of labour epidural analgesia (tEDA) with local anaesthesia and fentanyl mixture, and work shift for ECS at Danderyd Hospital, Sweden. In total, 135 ECS were analysed: 92% were delivered within 30 minutes. Mean DDI for all CS was 17.3 ± 8.1 minutes. With GA DDI was shortened by 10 and 13 minutes compared to SA and tEDA ($p<0.0005$). DDI for SA and tEDA was similar. No difference in DDI was seen regarding time of day or weekday. Apgar <7 at 5 min. was found more commonly in ECS having GA (11/64) vs. SA (2/30) and tEDA (1/41)($p<0.05$).

Conclusions: Low dose ITM has an important role mainly in a fast track concept to minimize systemic opioid consumption and still optimize postoperative analgesia in elective and emergent CS in recommended dose of 100 μg and hysterectomy 200 μg. If spinal labour analgesia is chosen addition of ITM doses 100 μg or less seems of no value to prolong the duration. ITM is widely used in Sweden in mainly CS and hysterectomy, although still restricted in some units due to fear of respiratory depression and/or difficulties monitoring postoperatively. Respiratory monitoring with polygraphy in obese mothers after CS ITM anaesthesia did not reveal severe sleep disorder breathing and seems to be of limited value in the postoperative period after CS performed in spinal anaesthesia including morphine. We found 92% of ECS, were delivered within 30 min. and DDI was shortened with GA by 10 and 13 minutes compared to SA and tEDA but with no difference between SA and tEDA.

LIST OF SCIENTIFIC PAPERS

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IV. Anette Hein, Jan G. Jakobsson
Portable respiratory polygraphy monitoring of obese mothers the first night after caesarean section with bupivacaine/morphine/fentanyl spinal anaesthesia.
Submitted

V. Anette Hein, David Thalen, Ylva Eriksson, Jan G. Jakobsson
The decision to delivery interval in emergency caesarean sections: Impact of anaesthetic technique and work shift. F1000Research 2017, 6:1977. doi: 10.12688/f1000research.13058.1

CONTENTS

LIST OF ABBREVIATIONS

AHI	Apnoea hypopnea index
ASA	American Society of Anesthesiologists Physical Status Classification System
BMI	Body Mass Index kg/ m^2
BP	Blood pressure
CI	Confidence interval, an interval estimate of a population parameter used in statistics
cm	Centimeter 10^{-2} meter
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CS	Caesarean section
CSE	Combined spinal-epidural technique
DDI	Decision to delivery interval
ECS	Emergency caesarean section
ED50	Effective dose (ED) in pharmacology, the dose of drug that produces a therapeutic response in 50 % of the subjects taking it.
EDA	Epidural anaesthesia
ESS	Epworth Sleepiness Scale
F	Fentanyl
g	Gram
G	Gauge, measure of needle size, higher G - smaller size
GA	General anaesthesia
GCP	Good clinical practice
h	Hour, hours
HR	Heart rate
5HT3	5hydroxytryptamine
i.v.	Intravenous injection
IQR	Interquartile range
IT	Intrathecal
ITM	Intrathecal morphine
kg	Kilogram 10^3 gram
kPa	Kilo Pascal, 1 kPa = 7.500617 mmHg
L3-L4	Interspace between lumbar spinal vertebra 3 and 4
M	Morphine
m., min.	Minutes
MAC	Minimal alveolar concentration
mg	Milligram 10^{-3}gram
ml, mL	Millilitre 10^{-3} litre
mm Hg	Millimeter of mercury, 1 mmHg = 0.133322 kPa
n	Number
NICE	The National Institute for Health and Care Excellence
NMDA	*N*-methyl-d-aspartate
NRS	Numeric rating scale
ns	None significant
NSAID	Nonsteroidal anti-inflammatory drugs
ODI	Oxygen desaturation index
OR	Operating room

OR	Odds ratio
OSA	Obstructive sleep apnoea
PACU	Post-anaesthesia care unit
PCA	Patient-controlled analgesia
PCO_2	Partial pressure of carbon dioxide
PDPH	Postdural puncture headache
pH	Potential of hydrogen, a numeric scale used to specify the acidity or basicity of an aqueous solution, *a=arterial*
pH*a*	
pKa	The logarithmic constant of acid dissociation
PONV	Post-operative nausea and vomiting
RA	Regional anaesthesia
RCT	Randomized controlled trial
RR	Respiratory rate
S	Sufentanil
SA	Spinal anaesthesia
SD	Standard deviation
SFAI	The Swedish Society for Anaesthesia & Intensive Care
SFOAI	Swedish Society of Obstetric Anaesthesia and Intensive Care
SPA	Spinal anaesthesia
SpO_2	Oxygen peripherial saturation
SPOR	Swedish Peri-Operative Register
SBAR	Standardised report; Situation, Background, Assessment, and Recommendation
TAP	Transversus abdominis plane block
$TcCO_2$	Transcutaneous (partial pressure) carbon dioxide
tEDA	"top-up" of labour epidural analgesia to surgical anaesthesia
UK	United Kingdom
VAS	Visual analogue scale
vs.	versus
µg	Microgram 10^{-6} gram

1 INTRODUCTION AND RATIONALE

Pain during labour and postoperative after CS and hysterectomy is not only unpleasant and causes reduced wellbeing but has also a direct impact on complications, recovery, time in hospital and development into persisting pain (1-3). The mother might choose an elective CS next time if the first vaginal birth experience was painful. Thus apart from a human perspective there are also economic incentives to minimize pain during these procedures.

There are several ways to reduce pain. During vaginal birth, neuroaxial analgesia is proven to give the most effective pain relief (4). Systemic opioids are shown to have limited effect on pain during labour but in neuraxial route opioids are proven effective (5-7). There is increased request for pain relief during labour. Single shot spinal analgesia is an alternative to epidural analgesia during labour, easier to administer and with faster onset of pain relief but with a restricted duration as limitation.

The majority of CS's are performed in single shot spinal anaesthesia. Addition of a low dose ITM is proven to create good, long lasting pain relief and is regarded as golden standard. Still it came to our knowledge that several units chose not to use addition of ITM in spinal anaesthesia for CS.

In abdominal hysterectomy spinal anaesthesia with sole bupivacaine and sole ITM has shown to reduce the postoperative morphine consumption vs. general anaesthesia in order to enhance fast recovery (8, 9). Several doses of ITM have been used in this setting but to us there were no known studies comparing effects of the different doses of ITM when added to bupivacaine.

Administration of morphine, no regard to whether by intravenous, intramuscular or neuraxial route, may result in side effects such as nausea and vomiting, pruritus, sedation and, although rare, the most feared side effect, respiratory depression. Respiratory depression may be delayed, thus how and for how long time patients should be monitored, after receiving neuroaxial morphine, is discussed. The opioid, the dose, and route of administration do impact the risk of respiratory depression and the benefit vs. risk should be thoroughly addressed. There are also other factors that may increase risk of side effects. Obese mothers have been found to develop respiratory depression to a greater extent than mothers of normal weight after caesarean section in spinal anaesthesia including morphine (10).

The rationale for this thesis was to achieve better knowledge about effects of different low doses of ITM in clinical use during labour and perioperative and postoperatively, whether addition of a low dose of ITM would prolong duration of single spinal labour analgesia and what dose of ITM would decrease postoperative intravenous patient controlled morphine analgesia without increasing side effects. We were interested in to what extent ITM is routinely used in Sweden and what is limiting its use. We aimed at observing respiratory pattern postoperative after CS performed in spinal anaesthesia in the obese cohort and sort

out whether polygraphy would be of use to identify respiratory depression in this setting. We studied the role of neuroaxial anaesthesia including ITM, in emergency category 1 and 2 CS.

Better knowledge about the effects of ITM doses, routine use and the reasons why some choose not to use ITM, role of respiratory depression after ITM could contribute to improve prevention and treatment of pain in labour, CS and hysterectomy.

2 BACKGROUND

2.1 PAIN

The International Association for the study of Pain IASP, defined pain 1979 as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. IASP further states “as pain always is unpleasant it is therefore also an emotional experience. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life” (11)

Pain perception begins in the periphery with stimulation of sensory nerves, further conducted via a complex series of nociceptive transmissions, resulting in generation of action potentials within the spinal cord and synaptic transmission to other supra spinal sites (12).

Mechanical, chemical and thermal stimuli activate sensory (nociceptor) neurons causing nociceptive pain, that signals intensity, localisation and duration of the stimulus and pain is reduced, disappear, when the stimulus is removed (13). When there is a surgical wound there will be inflammatory pain ongoing until the wound has healed. Peripheral sensitisation is caused by tissue injury and inflammation with release of sensitising inflammatory mediators causing lowered threshold of the innervating sensory neurons in the damaged tissue (13). Central sensitisation is caused by enhanced excitability of CNS neurons and results in intensified responses and spread sensitivity to normal sensory inputs.

If nerves are injured or sensory transmitting systems in the brain and spinal cord, this will cause neuropatic pain. Neuropatic pain is characterized by sensory loss in the area innervated by the nerve, but some individuals also develop spontaneous pain, hypersensitivity and dysaesthesia, triggered by slight stimuli like light touch.

The patient senses pain through the afferent pain pathway, which can be altered by various pharmacologic agents. Somatic pain-transmitting A-delta nerve fibres, enter the spinal cord through the dorsal roots, and terminate in a dense network of synapses, in the ipsilateral laminae I and II of the dorsal horn. There is minimal rostro-caudal extension of those fibers. Visceral C-fibers terminate in a loose network of synapses in the dorsal and ventral horn and cross over to the contralateral side with extensive rostro-caudal extension of fibers. This underlies the more diffuse localization of visceral pain versus somatic pain.

Pain experienced in labour and postoperatively after CS and hysterectomy is influenced by multiple physiological and psychosocial factors.

2.1.1 Labour Pain

Historically, and sometimes still, labour pain has been described as minor but by a questionnaire in 1984 Melzack found labour pain to be rated as painful as a digit amputation performed without anaesthesia, by nulliparous women without childbirth training (14). Nulliparous women with childbirth training scored lower pain but still high level of pain (14).

Pain experienced during first stage of labour is primary caused by cervical distension and transduced by afferents in the cervix and lower uterine segment rather than the uterine body. The visceral utero-cervical C-afferents enter the spinal cord in the region 10^{th},11^{th} and 12^{th} thoracic and 1^{st} Lumbar spinal segments and terminate in the deep dorsal and ventral horn and cross the midline to the contralateral side. The pain is diffusely localized. As labour progresses the pain usually increases and pain during second stage of labour is transmitted by the same afferents activated during first stage with addition of somatic afferents that innervate the cervix vaginal surface, vagina and perineum, via the pudendal nerve to the 2^{nd}, 3^{rd} and 4^{th} sacral spinal segments. The pain is more localized and reflects distension, ischemia and injury in the innervated area.

Apart from being unpleasant, pain during labour may influence labour and obstetric course. Increased secretion of epinephrine may cause beta-adrenergic tocolysis meaning inhibition of uterine contractions. Severe pain and fear may lead to the woman deciding to have an elective caesarean for the current or the following pregnancy. Labour pain may also continue as persisting pain when it is suboptimal handled (15).

2.1.2 Postoperative pain

There are a lot of different factors involved in the severity of experienced early postoperative pain, such as psychological, social and somatic factors together with operational technical and handling of pre-, peri-, and postoperative pain and anxiety. Women are found to suffer from higher postoperative pain vs. men (13).

Surgical pain is due to inflammation from tissue trauma or direct nerve injury (i.e., nerve transaction, stretching, or compression). Pain impulses are transmitted by A-delta and C-fibers and result in an experience of combination of localized somatic pain and more diffuse and dull visceral pain. Pain after CS and abdominal hysterectomy is depending on surgical technique, and approach for abdominal access, Phannenstiel or midline. Pain is mediated from the entire surgical field, abdominal wall, peritoneum and uterine fixation apparatus. It enters spinal cord on a wide range of segments. The dorsal roots affected during open hysterectomy are thus larger in numbers as compared to labour pain. Hysterectomy can also be performed with laparoscopy technique usually with reduced postoperative pain due to less traumatic surgery.

2.2 HANDLING OF PAIN

Pain can be managed by a variety of drugs and techniques. Oral administration of pain-medication such as paracetamol and NSAIDs e.g. ibuprofen is commonly available as over the counter analgesics. The combination of paracetamol and NSAID is also the first step on the escalating pain management staircase of multimodal pain management of postoperative pain. The concept of multi-modal or balanced analgesia combining analgesics with different

modes of action and side effects all aiming at minimizing the opioid need and opioid related side effects, morphine sparing analgesia has become standard of care (16).

Opioid analgesics e.g. morphine, administrated orally or intravenously, are mainly used for intense pain. Patient Controlled Analgesia, PCA morphine is common practise and often next step on the pain-staircase.

Local anaesthesia infiltrated or in a regional block e.g. Transversus Abdominis Plane (TAP) block can contribute to extra pain relief and is recommended to decrease systemic opioids (17).

Spinal or epidural local anaesthesia, often with morphine/morphine analogues added, thus providing both intra- and postoperative analgesia, is an attractive alternative in order to provide good pain relief with low incidence of side effects.

Ketamine, gabapentin or pregabalin are other drugs that have become popular to minimize the extent of neuropathic component in postoperative pain.

2.3 PERSISTENT PAIN

Postsurgical persistent pain resembles neuropathic pain and is probably often caused by damaged nerves, but there are also patients suffering from continuous inflammatory pain. Studies confirm that previous pain and the intensity of experienced early postoperative pain correlates with the risk of developing persistent postsurgical pain (13).

There are studies documenting that 4-10 % of vaginal births are followed by chronic pain problems (15). Eisenach et al. found 1 of 13 women suffering from severe acute pain after vaginal delivery, and that acute postpartum pain was a large independent risk factor for persistent pain (18).

Chronic pain may emerge after caesarean delivery and is influenced by the extent of acute post-operative pain (2). Eisenach et al. found 1 of 5 women suffering from acute post-operative pain after CS and in line with postpartum pain after vaginal delivery, acute post-operative pain after CS was a large risk factor for persistent pain (18). Incidence of persistent pain 8 weeks post-partum was 9.8% with no significant difference regarding mode of delivery, vaginal versus caesarean delivery (18).

One year after hysterectomy persistent pain was found in an incidence of 32% (19). Chronic pain was defined by Brandsburg et al. as ”having pelvic pain within the last 3 months”, in the questionnaire sent to 1299 patients, and answered by 90.3 %. 13.7% had pain more than 2 days a week. In a follow up review the authors found chronic pain problem is reported by 4.7–31.9% after hysterectomy in 11 identified studies (19). More pronounced postoperative pain is a risk factor for persisting pain. Spinal anaesthesia during hysterectomy was associated with lower frequency of chronic pain (3).

2.4 OPIOIDS FOR NEUROAXIAL USE

The most common opioids used as adjuncts in spinal and epidural analgesia today are the naturally occurring, by poppy plant synthesized morphine, semisynthetic diamorphine (not in use in Scandinavia) and synthetic phenylpiperidines like fentanyl and sufentanil.

Small doses of intrathecal morphine (ITM) was described 40 years ago to produce profound analgesia with no effect on motor function, while similar doses given systemically had negligible effect, showing a direct spinal mechanism of ITM (20).

Opioids bind to and activate opioid receptors that subsequently inhibit calcium channels and ascending nociceptive stimuli from the dorsal horn of the spinal cord.

Morphine, fentanyl and sufentanil in low doses bind to the μ-opioid receptor and mediate analgesia but also side effects like sedation, decreased gastrointestinal transition and respiratory depression (12).

2.4.1 Pharmacology

There are important pharmacological differences between opioids, like lipid- and hydro-solubility (=lipo- and hydro-philicity), molecular weight, pKa and protein binding. These biochemical properties have impact on kinetics, time to onset and offset of action. There is also different potency between the opioids. The differences in kinetics and potency have major influence on the clinical analgesic properties. Morphine is hydrophilic with low lipid solubility, 1.4 expressed in octanol-water partition coefficient to compare with high lipid solubility with fentanyl, 816, and further high with sufentanil, 1727. More rapid onset of analgesia is seen with higher lipid solubility. When an opioid is administered in the epidural space it first diffuses through the dura and arachnoid membranes, via the cerebrospinal fluid (CSF) and pia membrane, to the spinal cord and further through the white and grey matter to finally reach the dorsal horn with the μ-receptors which is the site of action. Uptake into epidural fat or systemic circulation is competing processes that limit the diffusion to the spinal cord. Lower pKa, and lower percent of protein binding results in a larger share of uncharged form of the opioid at body pH of 7.4, that penetrates the dura more easily. The pKa and protein binding percent for morphine, fentanyl and sufentanil is 7.9/ 35, 8.4/ 84 and 8.0/ 93 respectively. Hydrophilic opioids like morphine move rapidly within CSF and do not return to the epidural space, such as lipophilic opioids that redistribute to a large extent and are absorbed systemically from the epidural fat.

2.4.2 Doses

In 1979 Samii et al. reported about ten patients in pain that were given 20 mg morphine intrathecally with onset of analgesia at 26 ± 4 minutes and duration of analgesia for 27 ± 2 h, proposing a direct spinal opioid effect (21). The 20 mg single shot morphine dose is high also for intravenous administration and the intrathecal administration of one single direct injection

of this dose is huge, it is a dose that is 100 – 400 times greater than the doses used intrathecally commonly today illustrating a large therapeutic interval.

The same year Wang et al. published a study where eight patients with severe back pain secondary to malignancies received ITM, 0.5 – 1.0 mg, and achieved complete pain relief during 12 to 24 hours. Increasing the morphine dose from 0.5 to 1.0 mg did not prolong the relief of pain proportionately. The writers propose the technique may be used for obstetric analgesia or postoperative pain (22).

Today intrathecal opioids are widely used for analgesia. Earlier studies used mostly ITM as a sole analgesic in greater doses, while later trials use a combination of local anaesthetic, smaller doses ITM and/ or a lipid soluble opioid in order to get sufficient analgesia and still minimize side effects especially since some of the side effects are potentially severe. In obstetric and gynaecological anaesthesia low dose combined mixture has been shown to be effective in labour analgesia and as postoperative analgesia in caesarean section and abdominal hysterectomy. Tables with listed studies of intrathecal anaesthesia for labour and post abdominal hysterectomy pain show the development and different results (Table 16 and 17).

2.4.3 Side effects

Large doses of ITM is associated with a high incidence of side effects (6). Pruritus is the most common side effect and is described as dose related (6). Nausea and vomiting occur commonly postoperatively and during labour and it is therefore difficult to determine to what extent nausea and vomiting is a direct side effect of neuroaxial analgesia. Ondansetron is commonly administrated as prophylaxis and as treatment of postoperative nausea and $5HT_3$ antagonists have also been used to treat pruritus and shown to reduce the incidence of severe pruritus (23).

2.4.3.1 Respiratory depression

The most feared side effect of opioids is sedation and respiratory depression that can be seen regardless of route of administration. Early respiratory depression is observed when lipophilic opioids are administered intrathecally or epidurally, with a short time frame as the elimination rate is similar with the intravenous rout. However hydrophilic opioids like morphine stay in CSF for several hours, with rostral migration and absorption into respiratory centers in the brainstem, and can cause late respiratory depression up to 12 h after administration. American Society of Anaesthesiologists recommend monitoring of ventilation, oxygenation and level of consciousness in patients receiving opioids and for morphine to be performed hourly for 12 h after administration, and every second h for the next 12 h. The low but serious risk of late respiratory depression must be acknowledged whenever intrathecal or epidural opiates are administered. There are risk factors for respiratory depression to identify and consider such as advanced age, cardiopulmonary disease, operation, obesity and obstructive sleep apnoea. The incidence of respiratory depression in obstetric patients after neuroaxial morphine is 0-0.9% (24). Aboulish et al.

found 8/856 cases of respiratory depression, defined as <10 breath/min or desaturation < 85% on room air, in a study on CS in spinal anaesthesia including 200 μg ITM (10). All 8 mothers were obese (105 ± 2.1 kg) and the respiratory depression during sleep was not reversed by treatment with naloxone (10). Kato et al. retrospectively reviewed CS having 150 μg ITM and found 6/1915 patients experiencing bradypnea, respiratory rate (RR) ≤ 10 breaths/min; one obese with BMI 35, having OSA, with the same respiratory pattern during following nights (25). To our knowledge there are no studies of postoperative respiratory compromise conducted, explicitly assessing risk in obese mothers after CS. In a retrospective study of 5036 mothers having CS in spinal or epidural anaesthesia including morphine, 63% of the patients were obese (26). Crowgey et al. defined respiratory compromise with need for naloxone as oxygen saturation <90%, RR≤8 breaths / minute or value of <-2 on Richmond Agitation Sedation Scale and found no such event (26). There are multiple definitions used in studies assessing risk of respiratory impairment of opioids (27). There is a lack of clear definition of what a significant clinically respiratory impact caused by ITM is, and what kind of monitoring that is best catching any clinically respiratory impairment of importance (28). In a review regarding risk, prevention and monitoring of respiratory depression caused by spinal/ epidural morphine use in obstetric anaesthesia, Carvalho supports monitoring of sedation and RR up to 24 hours after neuroaxial morphine injection in low risk mothers, complemented with oxygen saturation in high risk cohort like obese mothers (24).

2.4.4 Labour analgesia

There are several different ways to handle labour pain but epidural and spinal analgesia are the most effective methods (29). Continuous epidural analgesia is today the most common neuroaxial method, sometimes initiated with a spinal as combined spinal epidural analgesia. However this thesis focus mainly on use of ITM and thus pharmacologic aspects in epidural labour analgesia will not be further reviewed. Single spinal labour analgesia is indicated when analgesia is required shortly before vaginal delivery. Advantages are that it is a technically simple and fast method to reach rapid onset of analgesia including sacral analgesia with low drug doses. The limited duration is the main disadvantage.

Historically neuroaxial labour analgesia started with injection of 0.01g Cocaine in single spinal in 1900 by Kreis, who stated: "*the impression gained from the medullary narcosis in parturients is remarkable. Loss of sensation to pain with maintained mobility and unclouded sensorium is most unusual."*(30). Stone, also using cocaine in single spinal for labour analgesia, concluded in 1901: *"For, with but little practice, any physician can become competent to perform the lumbar puncture"*(31). Sole morphine in single spinal was used early in obstetric neuroaxial analgesia. Table 16 shows studies of ITM for labour analgesia. Scott et al. published in 1980 a study of 12 patients in labour, who received 1.5 mg ITM as a sole agent, and observed abolished pain during first stage of labour and abolished pain during second stage for four patients and reduced for three (32). Though the used morphine dose was high by our norm, the side effects including itching of the face, nausea and vomiting, and frontal headache, were described as mild and simply treated (32). Baraka et al. compared in

1981 1 mg with 2 mg of ITM in labouring women and found onset to be between 15 to 60 min. and duration between 8 to 11 hours but described in contrast to Scott et al. that the majority of patients had somnolence, nausea, vomiting and pruritus (33). In 2001 Yeh et al. used a far lower morphine dose in labouring women with a combination of intrathecal bupivacaine 2.5 mg and fentanyl 25 μg with or without 150 μg morphine, and found the duration significantly prolonged in morphine group, but still adverse effects did not significantly differ between groups (34).

2.4.5 Caesarean section

In spinals for caesarean section a combination of ITM and local analgesic was introduced early. Abboud et al. showed in 1988 that 100 – 250 μg morphine combined with bupivacaine 0.75% was effective in reducing postoperative pain after caesarean section with minimal or no side effects (35). Several trials performed conclude intrathecal morphine 75-100 μg combined with bupivacaine 0.5 % 10-15 mg for CS is sufficient in reducing post caesarean section pain (36-38). Combining hyperbaric bupivacaine with low dose of a lipophilic opioid, with rapid onset to enhance intraoperative and first postoperative hours analgesia, and a hydrophilic opioid in order to prolong the duration of postoperative pain relief in a multimodal analgesia approach including paracetamol and NSAID is often used and recommended for CS spinal anaesthesia (39-41).

2.4.6 Hysterectomy

In abdominal hysterectomy Sarma et al. tested in 1993 three different doses of intrathecal morphine: 100, 300 and 500 μg given after the operation and used no local anaesthetic and found better analgesia in all morphine groups, best in 300 and 500 μg but no better analgesia in 500 group compared with 300 (9). Nausea and vomiting occurred most in 0-group, and least frequently in 300-group. Pruritus was seen only in morphine groups, most in 500-group (9).

In 1996 Wang et al. compared general inhalational with spinal anaesthesia including sole bupivacaine 15 mg for low abdominal women surgery and found spinal anaesthesia providing both perioperative anaesthesia and less post-operative pain first 24 h (8).

2.5 OBSTRUCTIVE SLEEP APNOEA

Obstructive sleep apnoea is a state when upper airway collapse and obstruction during sleep occur with usually snoring, oxygen desaturation and arousal from sleep. Screening for obstructive sleep apnoea is commonly performed with portable at-home polygraphy monitoring equipment, with collection of information about gas flow, saturation and thoracic and abdominal movements. Using defined algorithms this information is then transformed into indices: apnoea-hypopnea index (AHI) and oxygen desaturation index (ODI).

Apnoea: America Academy of Sleep Medicine defines apnoea as a drop in the polygraphy peak signal excursion by ≥90% of pre-event baseline airflow signal with duration ≥10 seconds (42).

Hypopnea: is classified as a drop in peak signal excursion by ≥30% of pre-event baseline airflow signal lasting ≥10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal (42).

The apnoea/hypopnea index (AHI): is the number of apnoea/hypopnea events registered per hour, and are graded into three categories of Obstructive Sleep Apnoea (OSA):
Mild OSA: AHI of ≥5 and <15,
Moderate OSA: AHI ≥15 and <30 and
Severe OSA: AHI ≥30.
Zero to <5 is commonly assessed as *normal*.

Oxygen desaturation: any event with a 3 % drop in blood oxygen levels, and the index (ODI) is the number of desaturation episodes per hours (42).

The screening and assessment for sleep apnoea is updated in JAMA 2017 and criteria have not changed (43). The polygraphy equipment software used in study IV is screening for both the AHI and ODI, Embletta (ResMed Sweden AB, Kista Sweden)/ Nox Sleep monitor (Nox Medical, Iceland) (44, 45). The program also provides, minimum blood oxygen saturation (SpO_2) level measured, during each desaturation episode, called the oxygen desaturation episode *nadir*.

Transcutaneous measurement of partial pressure of oxygen (SpO_2) **and carbon dioxide** ($TcpCO_2$ or $TcCO_2$) is an alternative method to explore breathing disorders (Tosca Radiometer Medical ApS, Denmark).

Epworth Sleepiness Scale (ESS)(46): a questionnaire used for screening for obstructive sleep disorder; is graded:
0-5: Lower Normal Daytime Sleepiness,
6-10: Higher Normal Daytime Sleepiness,
11-12: Mild Excessive Daytime Sleepiness,
13-15: Moderate Excessive Daytime Sleepiness and
16-24: Severe Excessive Daytime Sleepiness.

Among women of reproductive age the prevalence of OSA is approximated to 5-6% and in overweight parturients with BMI 25-30 there is a twofold increase in risk compared to women of normal weight during pregnancy (47, 48). In Sweden obesity is increasing, also seen in pregnancy but not yet reaches the incidence of USA or UK. In 2013 25% of pregnant women in Sweden were overweight and 13% obese with variation for different parts of Sweden. In Stockholm 8,7% were obese (49).

2.6 RESPIRATION DURING PREGNANCY

The pregnant woman has several physiological changes regarding ventilation due to increased levels of hormones. The upper airway may be narrowed by hyperaemia, airway mucosal oedema and vasomotor rhinitis is caused by rise in oestrogen. On the other hand rise in progesterone enhances sensitivity to carbon dioxide resulting in stimulated respiratory drive with increased minute ventilation and respiratory alkalosis.

2.7 EMERGENT CAESAREAN SECTION

ECS can be performed during general or regional anaesthesia. Historically introduction of regional anaesthesia during CS lowered the anaesthesia maternal mortality. The risk difference has decreased from 17:1 for general anaesthesia versus regional anaesthesia during 1979-1990 to 1.7:1 during 1997-2002 mostly due to better handling of general anaesthesia and airway problems (50). A majority of maternal deaths associated with GA is however still due to intubation failure (50). Most often GA is chosen when start of operation, incision, is wanted within 15 minutes from decision, that is in the most urgent cases and in cases where RA not is recommended like in severe cases of haemorrhage or haemodynamic instability. In addition to risk-benefit in favour for RA, the effective post-caesarean analgesia provided when neuroaxial opioids are used, is to be considered. An urgent CS is a very dramatic event with high logistic and psychological demands on the whole team involved. There is a time recommendation that an urgent CS is to be performed with delivery within 20 – 30 min. after decision, Decision to Delivery Interval (DDI). Swedish Society for Obstetric Anaesthesia and Intensive Care (SFOAI) state an anaesthetist should be available within 5 min. where there is a delivery department, and option to start to operate within 15 min. from decision but all these timeframes are more like tools for auditing obstetric anaesthesia service and with little evidence to support medical benefit, though it is clear that some neonates need immediate delivery (51, 52). The degree of CS urgency is categorized by Lucas et al. into a four-graded scale to facilitate communication:
Category 1) immediate threat to life of woman or foetus;
Category 2) maternal or foetal compromise that is not immediately life-threatening;
Category 3) needing early delivery but no maternal or foetal compromise; and
Category 4) at a time to suite patient and maternity team (53).

2.8 ANNUAL BIRTHS AND ROUTINES

In Sweden 2014 annual birth-numbers were about 114000 and about 18% were delivered as CS; 46% as non elective CS (8.1% of births), and the rest as elective CS (54). In Danderyd hospital we had during 2016 10749 births and 2394 CS in the two delivery departments Danderyd and BB Stockholm, of which 1119 were emergent (47% of CS and 10.4% of births). We administered 4693 labour epidurals during 2016, that is 44% of all births but since 1174 had elective CS done, 49% of the patients going for vaginal births had labour

epidural. Our labour epidural routines are: as start-dose we inject in total 15 ml of bupivacaine 0.1% and sufentanil 0.5 μg/ml, and as maintenance midwifery administered 10 ml boluses at maternal request about up to hourly. Midwives are encouraged to contact anaesthesiologist if there is decreasing effect, or other problems with the epidural to keep an optimal analgesia.

Danderyd Hospital is apart from the delivery units a large emergency hospital with about 520 beds for general, orthopaedic and gynaecological surgery, internal medicine and cardiology. All anaesthesia services, including 8 beds of intensive care is managed by two anaesthesia specialists and one anaesthesia registrar in house on call. During on call time, there are at least three surgical teams, each consisting of: one anaesthesia nurse, one scrub nurse and one or two assistant nurses. One surgical team is reserved for the women's surgical department. Another surgical team from the general surgical department located in the same building and within reach of 1-2 min. will assist in case of obstetric emergency collisions. When the regular operation program is running, during daytime Monday- Friday, there is always one OR spared, ready for urgent CS. The primary OR for ECS is located central of the largest delivery department, on the same floor and close to the women's surgical department (within reach in 30–60 seconds).

2.9 LOWEST EFFECTIVE DOSE, BENEFIT VS. RISK

It is important to adjust the ITM dose to the lowest effective dose maintaining a reassuring benefit vs. risk profile. Effects of different low doses of ITM in combination with local anaesthesia for spinal anaesthesia for CS to reduce postoperative pain are well studied and documented. There are however sparse data around minimal effective dose as adjunct to local analgesic in labour and hysterectomy. Use of ITM has become well accepted in CS and lower abdominal surgery to improve the postoperative quality. The national praxis of its use as adjunct for spinal anaesthesia in CS and low abdominal surgery in Sweden has however not been studied. ITM is associated with a small but risk for respiratory depression that can compromise safety. In obese mothers there is a greater risk, even though still low risk, for respiratory impairment after ITM compared with normal weight. The monitoring of patients at risk is still not well defined and there is room for further studies around monitoring respiration in at risk patients. Portable polygraphy sleeping apnoea devices monitoring after CS in spinal anaesthesia including ITM have not been extensively explored. Spinal (SA) and top up epidural (tEDA) are potential alternatives in ECS to reduce the risk associated with emergent general anaesthesia. Time to establish surgical anaesthesia is of importance in the emergent setting and time limits are proposed. General anaesthesia is preferred in most urgent cases, but regional anaesthesia (RA) may be a safe option if situation allows. How routine practice utilising different anaesthesia based on clinical situation, GA and RA – SA or tEDA, including neuroaxial opoids- with regard to DDI time, keeping set quality limits is not extensively documented.

3 AIMS OF THE THESIS

This project aimed to gain knowledge of intrathecal morphine during labour and in caesarean section and hysterectomy.

Study I

To evaluate the impact of supplementing two intrathecal morphine doses: 50 and 100 µg and placebo control (saline) to intrathecal labour analgesia with bupivacaine 1.25 mg and sufentanil 5 µg on duration, in a double-blind placebo-controlled trial.

Study II

To evaluate the impact of supplementing three intrathecal morphine doses: 100, 200 and 300 µg and placebo control (saline) to hyperbaric bupivacaine 12 mg, on postoperative total accumulated consumed intravenous morphine, analgesic effect, and occurrence and severity of side effects, during the first 24 hours after elective abdominal hysterectomy under general anaesthesia.

Study III

To assess the routine use of intrathecal and epidural morphine in obstetric and gynaecological patients, factors that limit/holdback its use and postoperative monitoring after intrathecal morphine in Sweden.

Study IV

To assess postoperative occurrence of apnoea/hypopnea and oxygen desaturation events per hour (AHI and ODI) in obese mothers the first night after CS with bupivacaine/ morphine/ fentanyl spinal anaesthesia and evaluate the use of portable respiratory polygraphy, for respiratory monitoring in this at risk cohort.

Study V

To assess the impact of anaesthetic technique, general anaesthesia vs. regional spinal / epidural top up and work shift on the DDI in emergency CS, with a decided DDI <30 minutes at our hospital, Danderyd Hospital (emergency category 1 and most urgent category 2 CS).

4 METHODS

4.1 STUDY DESIGNS

Table 1. Overview of study designs, study populations and analyses.

	Study Design	Study population	Number	Analysis
Study I	Randomized placebo controlled double blind trial	Nulliparous women, ASA I – II, requesting epidural analgesia during spontaneous labour, cervical dilatation $\leq$ 7 cm	90 → 78 analysis	Log-rank analysis to compare median time of cumulative analgesic duration obtained from Kaplan–Meier analysis.
Study II	Randomized placebo controlled double blind trial	Women ASA I-II between 30 and 70 years of age, scheduled for abdominal hysterectomy with low transverse incision	144 → 136 analysis	Morphine requirement and VAS scores were analysed with nonparametric tests, Kruskal–Wallis analysis of variance, and Mann–Whitney U-test as appropriate
Study III	Questionnaire survey	Anaesthesiologists in charge of obstetric anaesthesia units in hospitals in Sweden.	47 → 32 responding	Descriptive
Study IV	Prospective postoperative explorative observational study	Parturients with BMI >30 kg/m^2 at the first antenatal consultation, who planned for elective CS with low transverse incision performed using standard spinal anaesthesia	23 → 20 analysis	Differences: with Student's t-test for continuous variables and Chi-squared test for categorical data
Study V	Retrospective chart review study, using a *proforma protocol*	Emergency CS needing the alarm, expected delivery immediately and up to a decision-delivery interval of 30 minutes	150 → 135 analysis	Comparing means: 2 variables Mann-Whitney U test > 2 or more groups Kruskal-Wallis H test Chi-square-test for categorical data.

Table 2. Overview of study designs, study populations, neuroaxial route of administered morphine, doses of morphine, neuroaxial mixture and primary variables.

	Study population, design	**Morphine neuroaxial route**	**Groups and dose of morphine** µg	**Other neuroaxial opioid and dose** µg	**Neuroaxial local anaesthesia and dose** mg	**Primary variable**
Study I	Labour analgesia RCT	Single spinal analgesia (CSE)	0 / 50/ 100 µg	Sufentanil 5 µg	Bupivacaine 1.25 mg	Duration of analgesia
Study II	Abdominal hysterectomy postoperative analgesia RCT	Spinal anaesthesia	0/ 100/ 200/ 300 µg	0	Bupivacaine hyperbaric 12 mg + Standard general anaesthesia	Postoperative consumed nurse administered + PCA i.v. mg morphine
Study III	Survey to Obstetric / Gynaeacol. anaesthetists	Morphine spinal / epidural anaesthesia				Use of neuroaxial morphine - Labour analgesia - Caesarean section - Abdominal hysterectomy
Study IV	Caesarean Section BMI > 30 Postoperative observational	Spinal anaesthesia	100 µg	Fentanyl 10 µg	Bupivacaine hyperbaric 11-12 mg	Postoperative occurrence of hypo/apnoea/ desaturation during sleep
Study V	Emergency caesarean section Retrospective chart review	Spinal / Epidural / General anaesthesia	SA: 100 µg EDA: 2 mg	SA: Fentanyl 10 µg EDA: Fentanyl 50-100 µg	SA: Bupivacaine hyperbaric 11-12 mg EDA: Ropivacaine 112 -150 mg	DDI and impact of chosen anaesthetic technique (GA /SA / EDA) and work shift

4.1.1 Study I

This randomized, doubled-blind placebo-controlled trial was conducted in Danderyd Hospital and Karolinska University Hospital.

Study population: Healthy nulliparous women, in spontaneous labour with a cervical dilatation ≤ 7 cm, requesting epidural analgesia in labour, were included. Only parturient with a term singleton foetus in the vertex position were included.

Randomization: Computer-generated blocked randomization for the two institutions was

performed into one of three groups: intrathecal morphine 50 µg (M50), 100 µg (M100), or an equal volume of saline (M0) each to be added to bupivacaine 1.25 mg and sufentanil 5 µg to a total volume of 2.5 mL.

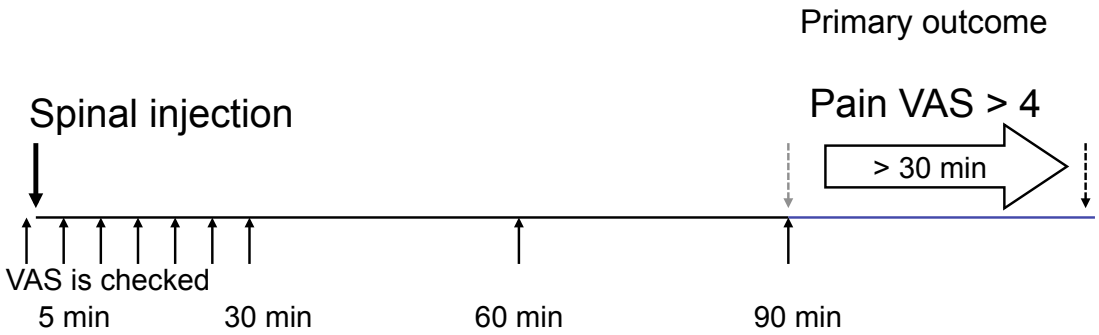
CSE was performed with a needle-through-needle technique at L3–4 or L4–5. The study solution was injected after observing free flow of cerebrospinal fluid. The spinal needle was then removed and the epidural catheter was inserted, not to be used during study period, but to ensure following pain treatment after the spinal analgesia had decreased and additional analgesia was requested.

Pain was monitored with a visual analogue scale (VAS) where 0 = no pain and 10 = worst possible pain. Women were assessed immediately before and at 5 min intervals after intrathecal injection for the first 30 min and then every 30 min until a VAS > 4 was observed, or additional analgesia was requested.

Analgesia onset time was defined as the time from intrathecal injection to VAS ≤ 4. Successful spinal analgesia was defined as VAS ≤ 4 within 30 min of intrathecal injection. **The primary outcome:** Duration of spinal analgesia was defined as the time from the intrathecal injection to VAS > 4 or request for additional analgesia. Secondary outcomes were onset time, occurrence of side effects and maternal satisfaction.

Sensory level to cold, assessed in the mid-clavicular line bilaterally, and motor blockade using a modified Bromage scale were recorded. Blood pressure, heart rate, pruritus, nausea, sedation and respiratory depression were documented and treated as required.

Figure 1. Primary outcome for Study I was duration of spinal analgesia. We set an extended duration of analgesia of more than 30 min to be of clinical value.



4.1.2 Study II

This randomized, doubled-blind placebo-controlled, trial was conducted in Danderyd Hospital (n = 100) and Karolinska University Hospital (n = 44) between 2005 and 2008.

Study population: Women, ASA I-II between 30 and 70 years of age, scheduled for

abdominal hysterectomy with low transverse incision, were included. Patients on regular pain medication, ASA III-IV, or contraindications to spinal anaesthesia were excluded.

Randomization: Computer-generated blocked randomization for the two hospitals was performed into one of four groups: intrathecal morphine, 100, 200, and 300 μg or an equal volume, 1 ml of saline as placebo as supplement to hyperbaric bupivacaine 0.5%, 2.4 ml (12 mg) to a total volume of 3.4 ml. All patients were included and completed the study before the randomization code was revealed.

Preoperatively all patients were given paracetamol 1.5 g orally, and paracetamol was continued with 1 gram every 6 hours according to the routines at our departments. Nonsteroidal anti-inflammatory drugs (NSAID) were not used. If needed, oxazepam was given as anxiolytic. Infusion of Ringer's acetate solution was initiated prior to spinal anaesthesia.

Spinal anaesthesia was performed with bupivacaine and study drug as described, using a 25 G pencil point needle in the L3-L4 or L4-L5 interspace after confirming free flow of cerebrospinal fluid.

Standard general anaesthesia was induced after sensory level to cold was checked. Fentanyl 0.1 mg, propofol 2–3 mg/kg, and atracurium 0.5– 0.6 mg/kg i.v. was administered and anaesthesia was continued, after tracheal intubation, with a mixture of oxygen and nitrous oxide – 30/70% with addition of sevoflurane to minimal alveolar concentration (MAC) 1–1.5. All patients received droperidol 1 mg and betametason 4 mg i.v. to reduce the incidence of post-operative nausea and vomiting. Morphine 0.1 mg/kg was administered i.v. 30 min. before ending operation, for good post-operative pain treatment. Time for extubation was considered time zero.

Pain was monitored with a visual analogue scale (VAS) where 0 = no pain and 10 = worst possible pain in the post-anaesthesia care unit (PACU). Patients stayed in the recovery area during the first post-operative night.

Rescue pain treatment, morphine 0.05 mg/kg, was administered i.v. if pain VAS > 4, by the nurse in PACU, every 5 min. until VAS < 4.

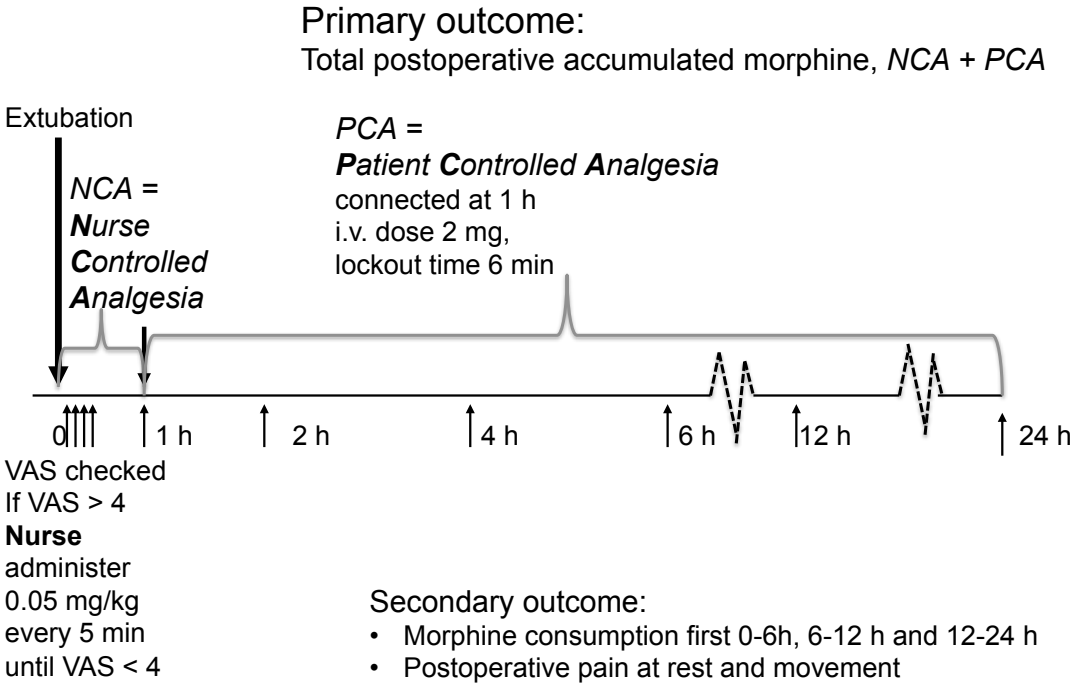
Morphine PCA was connected 1 h after end of anaesthesia when the patient was awake and able to use this. We programmed the PCA to administer boluses of 2 mg of morphine, with a lockout time of 6 min and maximum of 40 mg within 4 hours.

The primary outcome: the postoperative total accumulated amount of morphine consumed. The secondary outcomes were morphine consumption on the first 0–6 h, 6–12 h, and 12–24 h, postoperative pain at rest and at movement, nausea, pruritus, sedation, oxygen saturation, respiratory rate, heart rate and blood pressure.

Adverse events were treated according to the routines at our departments. Pruritus was treated with clemastin 2 mg i.v. Nausea and vomiting was managed with ondansetron 4 mg

i.v. which could be repeated. When pharmacological intervention for pruritus, nausea, and vomiting was administered to patients, they were considered to have experienced that side effect. Naloxone was to be provided at the discretion of the anaesthesiologist in case of respiratory depression, severe pruritus, or sedation.

Figure 2. Primary outcome Study II is total postoperative accumulated morphine consumption.



4.1.3 Study III

Population: Anaesthesiologists in charge of obstetric anaesthesia in the 47 delivery units in Swedish hospitals were invited to answer a questionnaire.

Collection of data: In December 2014 the questionnaire was sent by email together with a letter to the anaesthesiologists. In April 2015 this was repeated, with an additional postal mail to those clinics that had not replied. The clinics that did not return answer were phoned to ensure right anaesthesiologists were addressed. The survey was e-mailed in two versions: a Word document, to fill in and save by the computer, and return by email to a study email address, and a PDF-file to print and fill in by hand if this was chosen, and send by post to our hospital address.

The questionnaire consisted of 26 questions to reflect the routine use of morphine, fentanyl and sufentanil as supplement to local anaesthetic, in spinals and epidurals for CS, hysterectomy and other gynaecological operations, in the different units. Questions about the routine use of ITM for labour analgesia were also included. (Study III, questionnaire in English) The questionnaire contained both multiple choice and full written answers.

We asked for approximated numbers of CS and hysterectomies performed in spinal and

epidural anaesthesia, respectively, and numbers of patients administered with opioids, especially neuraxial morphine, including doses for the operations performed.

We asked for reasons behind excluding supplementation of intrathecal/epidural morphine when they have chosen not to use it.

Questions to reflect organisation of monitoring after intrathecal / epidural morphine administration, and occurrence of known serious adverse events in their units were also included.

4.1.4 Study IV

This prospective observational study was conducted in Danderyd hospital from December 2015 to October 2017.

Study population: Obese parturients, planned for elective CS with low transverse incision in standard spinal anaesthesia, were included after information and consent at the pre-anaesthetic consultation. Obesity was defined as BMI >30 kg/m^2 registered at the first antenatal consultation. Patients with diagnosed obstructive sleep apnoea (OSA) receiving treatment, like continuous positive airway pressure (CPAP) or mouth guard, any known contraindication to ITM or language difficulties were excluded.

All patients filled in a standardised Epworth Sleepiness Scale (ESS) questionnaire (46).

Preoperatively the patients received 1.5 g paracetamol orally, and paracetamol was continued postoperatively 1 g every six hours or 1.330g every eighth hours. Ibuprofen (400 mg) was administered every eighth hours.

Spinal anaesthesia was performed using a 25-gauge pencil-point needle with the patient in left lateral or sitting position, at the patients and/or anaesthetists' preference, according to standard routines for CS in our department. A mixture of hyperbaric bupivacaine (11–12 mg), fentanyl (10 μg) and morphine (100 μg), was injected intrathecally to all patients. Hypotension was prevented by our ordinary routines; left lateral position to reveal aorto-caval compression, co load of Ringer lactate and phenylephrine/ephedrine injections.

Routine monitoring after spinal CS anaesthesia in the postoperative and obstetric ward includes the following: heart rate and blood pressure; control of uterine contraction and bleeding; pain by NRS/VAS; urine output; control of sedation, and if sedated counting RR every hour; mobilization; and breast feeding. Patients are encouraged to mobilize, stand by the bed, at about 5–6 hours postoperatively. Urine catheter is usually removed after the first postoperative night. During the 3–5 first hours postpartum, the patients were continuously observed awake in the postoperative department.

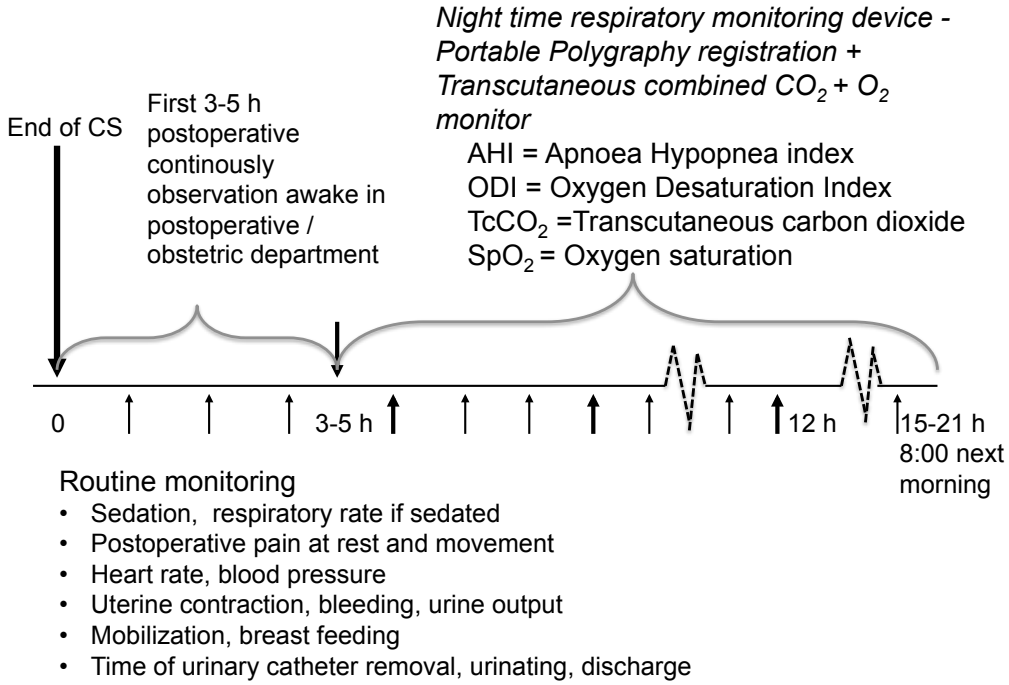
Extended postoperative study monitoring added to routine monitoring: a portable OSA polygraphy monitor with a finger probe to measure oxygen saturation, nasal catheter to

measure expiration flow and thoracic and abdominal strings to register breathing movements, (Embletta - ResMed Sweden AB, Kista, Sweden/Nox Sleep monitor - Nox Medical, Iceland); and a combined ear-probe for transcutaneous carbon dioxide ($TcCO_2$)/oxygen saturation (SpO_2) monitor (Tosca Radiometer Medical ApS, Denmark).

After the first 3-5 postoperative hours of routine monitoring, polygraphy and Tosca registration was applied during rest/sleep the first postoperative afternoon and night.

Adverse events such as pain NRS > 3, nausea and vomiting or pruritus were managed according to the department's routines.

Figure 3. Monitoring after CS in Study IV



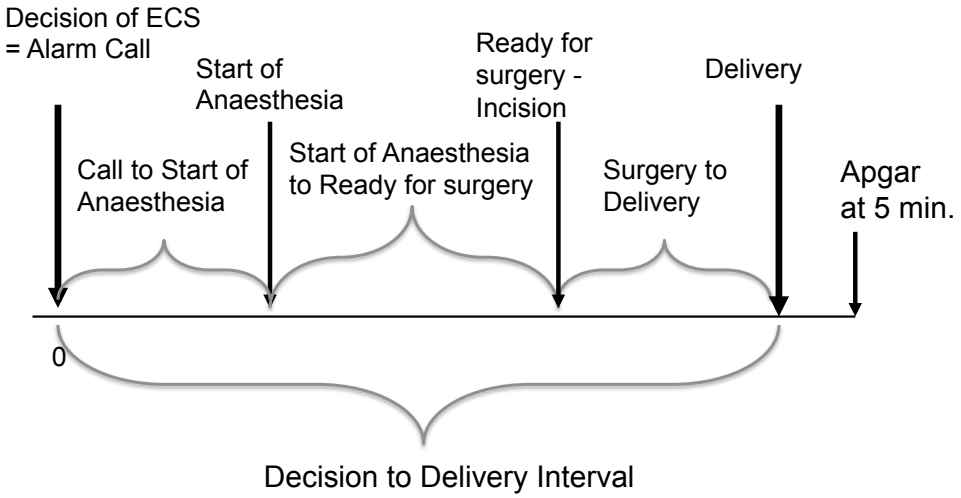
4.1.5 Study V

This is a retrospective chart review study using a *proforma protocol*. No intervention was initiated by or associated with the present study.

Study population: alarm logs and patient records for all ECS (category 1 CS and some urgent category 2 CS) at Danderyd Hospital from 1st of January to October 31st 2016 were collected and analysed.

Data collection: We retrieved time events; start time of anaesthesia, start and end of operation and type of performed anaesthesia from our electronic surgical registration system (Orbit 5.7) after matching time of the event from the ECS alarm logs. Time of delivery, the foetal status and neonatal need of treatment was collected from the patient journal.

Figure 4. Time events from Decision of ECS to Delivery, at time for decision expected delivery within 30 minutes.



When the obstetrician presses the alarm for ECS, at least one experienced anaesthesiologist is called together with anaesthesia and scrub-nurses and a neonatologist. We have been working with the alarm and communication process to facilitate use of regional anaesthesia.

Decision on ECS needing immediate delivery, in the most severe cases: The attending obstetrician presses the alarm gathering the surgical team together with anaesthesia specialist, anaesthesia registrar and neonatologist. The obstetrician follows the patient to hasten the process.

Decision on ECS needing delivery within 30 minutes, estimated by the obstetrician: The obstetrician first informs the anaesthesia specialist by phone with report by SBAR, including whether regional anaesthesia is an option and if there is a labour epidural to top-up, and then presses the alarm to gather the team.

Anaesthetic technique: The attending anaesthesiologist decides on anaesthetic technique according to routines at our department. When an immediate delivery is urged GA is recommended in most cases. GA is based on pre-oxygenation followed by a rapid sequence induction with propofol and suxamethonium, intubation and sevoflurane until delivery. When need for delivery is expressed within 30 min. spinal anaesthesia (SA) or top-up epidural (tEDA) is recommended. A rapid SA is chosen if there is time and a well working labour epidural anaesthesia is not established. SA is performed with hyperbaric bupivacaine (approximately 2.4 ml; 5 mg/ml), morphine (100 µg) and fentanyl (10 µg). Top-up of a well working labour epidural, is chosen when mother and child's status allow, with ropivacaine (approximately 15 – 20 ml; 7.5 mg/ml) and fentanyl (100 µg). The routine is to start the top up dose outside, but close to, the OR, within reach in 30-120 seconds, when it seems appropriate. This requires the anaesthesiologist to follow with the patient, to enable close, continued supervision.

4.2 STATISTICS

4.2.1 Study I

Power analysis: Based on former studies of the duration of single spinal labour analgesia with combinations of bupivacaine and fentanyl or sufentanil a power analysis was conducted (34, 55). We set an extended duration of analgesia of more than 30 min. to be of clinical value and with a power of 0.80 and $\alpha < 0.05$, 27 women in each group were required. The sample size was increased to 30 in each group, as we expected 10% dropout rate.

Analysis of results: Normally distributed continuous variables were compared using Students't-test or analysis of variance. Categorical data were analysed using chi-square test and Fisher's exact test. $P < 0.05$ was considered significant. To assess the cumulative proportion of continued spinal analgesia, Kaplan–Meier survival analysis was used. Log-rank analysis was then used to compare median time of cumulative analgesic duration obtained from Kaplan–Meier analysis. Spearmans' rang correlation was used to assess correlations.

4.2.2 Study II

Power analysis: We estimated morphine consumption in the control group to 40 mg for each patient and a standard deviation of 8 mg, based on former studies with spinal bupivacaine anaesthesia (12–15 mg) combined with general anaesthesia (56, 57). A 30% reduction of morphine consumption was assumed to be of clinical value. To detect a 30% reduction with a power of 0.80 and $\alpha < 0.05$, 33 women in each group were required. As we expected a 10% dropout rate, the sample size was increased to 36 in each group.

Analysis of results: Normally distributed continuous variables were compared by using Student's t-test or two-way analysis of variance. Morphine requirement and VAS scores were analysed with nonparametric tests, Kruskal–Wallis analysis of variance, and Mann–Whitney U-test as appropriate. Categorical data were analysed using Chi-square test and Fisher's exact test. $P < 0.05$ was considered significant.

4.2.3 Study III

Data is presented as number and percentage, and range as applicable. In order to put our results into perspective, with regards to the impact of routine use of opioids, we used annual total number of performed CS in the obstetric unit to approximate the size of the different units. We got the annual numbers from The Swedish Medical Birth Register from National Board of Health and Welfare (Sweden). We used no formal statistical tests in Study III.

4.2.4 Study IV

Data is presented as the mean and standard deviation; categorical data are presented as frequencies. The study is explorative and observational, thus no power analysis has been conducted.

Analysis of results: Differences have been studied with Student's t-test for continuous

variables and Chi-squared test for categorical data. Spearmans' rang correlation was used to assess correlations.

4.2.5 Study V

Descriptive statistics regarding the ECS and the variables was made using mean, standard deviation (SD) and range, as well as median and interquartile range (IQR), as appropriate.

Analysis of results: Mann-Whitney U test was used for comparing means between two variables and Kruskal-Wallis H test was used when comparing two or more groups. Chi-square-test was used for test of differences between categorical data. A p-value <0.05 was considered significant.

4.3 ETHICAL CONSIDERATIONS

Ethical permits have been obtained for **study I, II, IV and V** from Regional Ethics Committee in Stockholm, Sweden. Patients were accurately informed both verbal and in writing and provided written consent. **Study III** is a survey concerning only clinical practice and routines. No patient data was included. Ethical committee approval was not applied for, in accordance with Swedish ethical board guidelines and with the principles outlined in the Declaration of Helsinki.

Since **Studies I and II** include drug interventions, permits have been obtained from Medical Product Agency, Sweden as well, in accordance with GCP. **Studies I and II** are placebo (saline) RCT's and all patients got good pain-relief, the placebo groups had proven efficient component intrathecally as well, followed by epidural and PCA administration respectively. The practiced method, in **Study I**, Combined Spinal Epidural (CSE), is routinely used in delivery units, and does not show extra risks. CSE was used to ensure good pain relief during labour after spinal analgesia had diminished. **Study IV** implicate technical intervention with more extended monitoring than with routine care, that might affect ability of rest, sleep and contact with the new-born baby for mothers, first night after caesarean section. However the polygraphy equipment is small, made for home use, not invasive, and could be moved when mothers were awake so it would not interfere with breastfeeding and have minimal effect on the mother-and-child contact. Obese mothers have been shown at extra risk for respiratory impact postoperatively, and there is a lack of knowledge, thus we found it reasonable to accomplish the study. We preferred to start with an explorative observation study on this cohort at risk mothers, to find if further studies including control group would be warranted. We did not want to include mothers as controls before we had findings supporting further studies. The monitoring equipment and analysis of results were used and made in close cooperation with the well-established team in our department that do this on daily basis. **Study V** was retrospective with a *proforma protocol* or "prospective with no study-intervention" chart review with only neonatal data picked from patient journal and no individual identity-data collected and we found no ethical considerations.

5 RESULTS

5.1.1 Study I

We enrolled 48 labouring women from Danderyd Hospital and 42 from Karolinska University Hospital; 82 women obtained adequate pain relief from the intrathecal injection and 78 of these continued labour until return of pain, VAS > 4 and were included in final analysis of duration, with 26 in each group M0/M50/M100.

Inadequate pain relief from the spinal injection within 30 minutes, was reason to exclude eight women and four delivered before return of VAS > 4; two from the M50 group were delivered vaginally at 92 and 162 min, respectively. The other two were from the M0 group: one parturient had a normal vaginal delivery after 157 min and one had non-reassuring foetal heart rate pattern and thus urgent delivery by vacuum extraction. In the Kaplan–Meier survival curve for cumulative duration of VAS < 4 these subjects are shown as censored observations and otherwise excluded from statistical analysis of duration (Fig. 5).

Table 3 present maternal data, initial cervical dilatation and VAS before intrathecal injection. There were no significant differences between groups in duration of analgesia, onset time, subsequent epidural bupivacaine requirement, pruritus or maternal satisfaction (Table 4, Figs. 5 and 6). Onset time was not affected by the degree of cervical dilatation at entry to the study, Spearman's correlation coefficient, ($r = 0.187$; $P = 0.093$) nor was the duration of analgesia ($r = - 0.098$; $P = 0.39$) (Figs. 7 and 8). Time to onset or effective analgesia was not affected by the degree of cervical dilatation when the spinal injection was administered, no difference was seen between patients with cervical dilatation 3–5 and 6–7 cm.

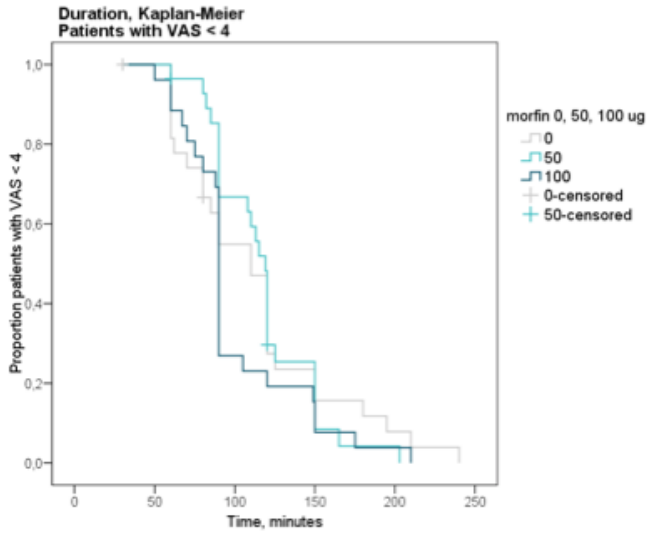
Oxytocin during labour was administered to most labouring women, with no difference between groups, the majority starting after spinal injection. There were no differences in obstetric and neonatal outcome (Table 5). No woman required treatment for hypotension, nausea, sedation or respiratory depression. No woman was reported having PDPH, four days after delivery. No significant differences between groups were found regarding satisfaction with analgesia; in fact all women answered either very satisfied or satisfied.

Table 3. Personal and baseline data

	M0 n=28	M50 n=28	M100 n=26
Age [years]	30 [22–37]	31 [22–38]	29 [20–40]
Weight (kg)	80 (11)	83 (11)	78 (9)
Height (cm)	166 (6)	167 (7)	168 (6)
Cervical dilatation at entry (cm)	5.0 [3–7]	5.0 [3–7]	4.5 [3–6]
VAS pre spinal	9.2 [8–10]	8.7 [6.5–10]	8.6 [6.5–10]

Data are median [range] or mean (SD)

Figure 5. Kaplan–Meier showing proportion of women with VAS ≤4 in M0, M50, M100 groups after intrathecal injection. Crosses represent subjects who delivered before return to VAS > 4. No differences between the groups.



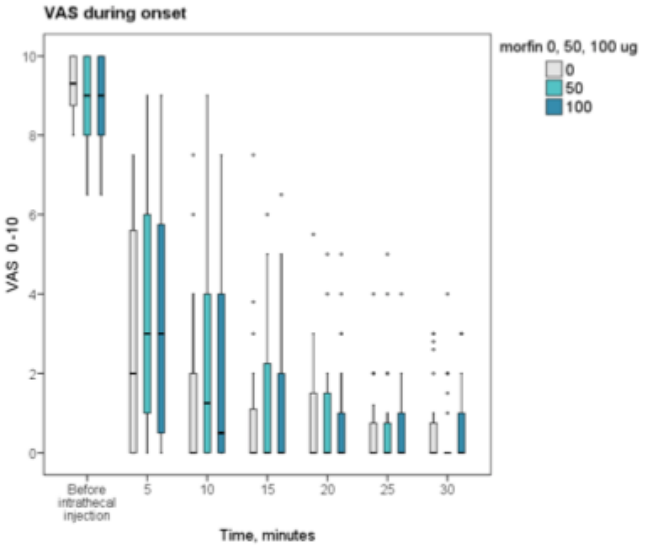
Duration
Mean ±SD

M0
113 ± 50

M50
116 ± 32

M100
100 ± 38

Figure 6. Box-plot of VAS during onset of analgesia in M0, M50 and M100 groups. Boxes show lower quartile, median and upper quartile. Dots represent outliers.
No differences between the groups.



Onset
Mean ±SD

M0
7.7 ± 4.4

M50
9.6 ± 5.1

M100
8.8 ± 5.5

Table 4. Spinal analgesia block characteristics

	M0	M50	M100
Onset (time to VAS≤ 4) minutes, Mean ± SD (n) [range]	7.7 ± 4.4 (28) [5–25]	9.6 ± 5.1 (28) [5–25]	8.8 ± 5.5 (26) [5–25]
Duration minutes Mean ± SD (n) [range]	113 ± 50 (26) [60–240]	116 ± 32 (26) [60–203]	100 ± 38 (26) [50–210]
Sensory block height to cold Median [range]	T7 [T4–T12]	T8 [T2–T10]	T7 [T4–T12]
Motor block Bromage ≥1 n (%)	1 (4)	2 (8)	0
Hypotension >20% n (%)	3 (11)	1 (4)	2 (8)
Pruritus n (%)	15 (58)	17 (61)	15 (58)
Maternal satisfaction %			
very satisfied	79	92	88
satisfied	21	8	12
Epidural requirement (mL/h) mean ± SD	4.9 ± 2.9	4.2 ± 3.1	6.9 ± 6.6

Data are mean ± SD, median [range] or number / %.

Figure 7. The figure shows the variation in onset time without correlation with cervical dilatation at entry to the study. (Spearman's correlation coefficient, (r = 0.187; P = 0.093)
Each dot may represent more than 1 patient.

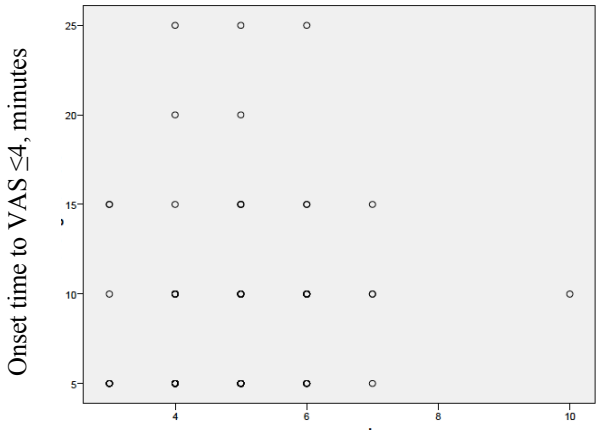


Figure 8. Cervical dilatation at entry to the study did not affect duration of analgesia (Spearman's correlation coefficient, (r = - 0.098; P = 0.39)

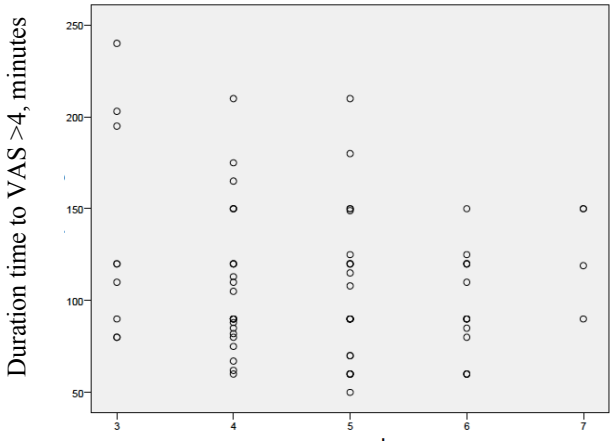


Table 5. Obstetric and neonatal outcome

	M0 n =28	M50 n =28	M100 n =26
Duration of labour, min.	456 (293)	424 (185)	376 (212)
Oxytocin infusion	26 [93]	26 [93]	26 [100]
Mode of delivery			
Normal vaginal delivery	14 [50]	19 [68]	17 [65]
Instrumental delivery	10 [36]	8 [29]	6 [23]
Caesarean section	4 [14]	1 [4]	3 [12]
Apgar score < 7 at 5 min	0	1 [4]	1 [4]
Umbilical artery			
pH	7.25 (0.14)	7.23 (0.16)	7.20 (0.11)
pCO_2	7.32 (1.65)	7.38 (1.66)	7.93 (1.63)
base deficit	6.49 (2.64)	7.24 (4.02)	6.80 (3.88)

Data are mean (SD), or number / [%].

5.1.2 Study II

Of the 144 women having abdominal hysterectomies in spinal anaesthesia including morphine during general anaesthesia enrolled, 136 were included in statistical analysis. Eight women were excluded from statistical analysis. Midline instead of Pfannenstiel incision was used in five patients. By mistake NSAID was administered to two patients and a wrong dose of ITM to one patient. The Consort flow chart for the study is shown in Fig. 9.

Demographics and perioperative data for the four groups were comparable (Table 6).

Postoperative morphine consumption: All three groups receiving ITM showed reduced accumulated 24 h post-operative morphine consumption (Table 7, Fig. 10). Analysing values as medians, morphine consumption vs. placebo was significantly reduced by Morphine 100 μg at 0–6 h, 6–12 h, and for the entire 0–24 h time interval post-operation (Table 7). Morphine consumption as compared with morphine 100 μg was further significantly reduced by Morphine 200 μg at 0–6 h and for the entire 0–24 h time interval post-operation (Table 7). We saw no further reduction of morphine consumption with morphine 300 μg and no difference regarding the quality of analgesia vs. morphine 200 μg. Analysing values as mean we found Morphine 100 μg reduced morphine consumption vs. placebo at 0-6 h and for the entire 0-24 time interval while Morphine 200 μg reduced morphine consumption vs. placebo at all-time intervals 0-6 h, 6-12 h and 12-24 h (Table 7, Fig 10).

Postoperative pain is shown in Table 8. A significant reduction in pain was observed when comparing the first 12 h pain VAS score between *all* three groups receiving ITM and the placebo control group, ($P < 0.05$). No difference was seen regarding pain at rest, VAS > 4 at any time point; 35% in the placebo group of patients and 18%, 22%, and 19% for the 100, 200, and 300 μg groups, respectively (Table 9). During movement the experience of pain, VAS > 4 was more common but still not significantly different between the groups; 47%, 24%, 32%, and 30% for placebo and morphine escalating dose groups, respectively (Table 9).

Adverse event observations: In 75% of patients minor peri-operative hemodynamic variations were treated with ephedrine, without differences between groups. No major adverse events or complications were seen during surgery or the 24 postoperative hours studied. Table 9 shows the incidence of side adverse events, with only small differences seen between the groups. Pruritus occurred solely in morphine groups. Nausea and vomiting were seen equally common in all groups (Table 9). No patient developed PDPH.

Figure 9. Consort

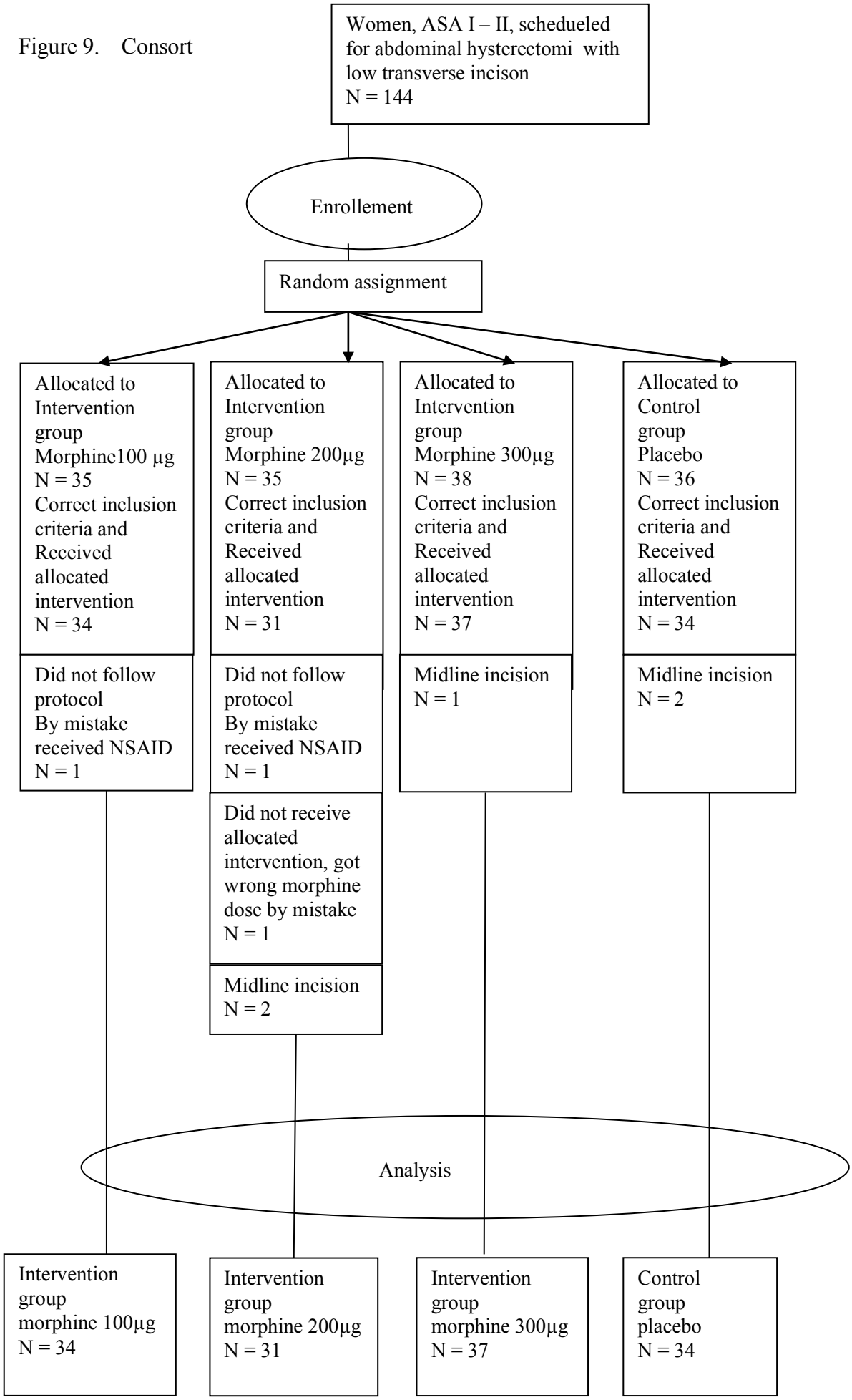


Table 6. Demographics and peri-operative data

	Placebo N = 34	M100µg N = 34	M200µg N = 31	M300µg N = 37
Age(yr)	51 ± 8 [38-69]	51 ± 8 [38-66]	49 ± 8 [39-62]	51 ± 8 [39-70]
Weight (kg)	71 ± 12	70 ± 9	71 ± 13	65 ± 8
Length (cm)	166 ± 6	166 ± 7	166 ± 6	165 ± 6
Duration of surgery (min)	95 ± 27	102 ± 29	101 ± 34	95 ± 32
Range	[42-163]	[60-170]	[50-175]	[40-180)]
Blood loss during surgery (ml)	307 ± 246	314 ± 221	316 ± 267	272 ± 320
Range	[0-1050]	[0-800]	[0-1300]	[0-1350]

All values are expressed as mean, SD [range], M=morphine

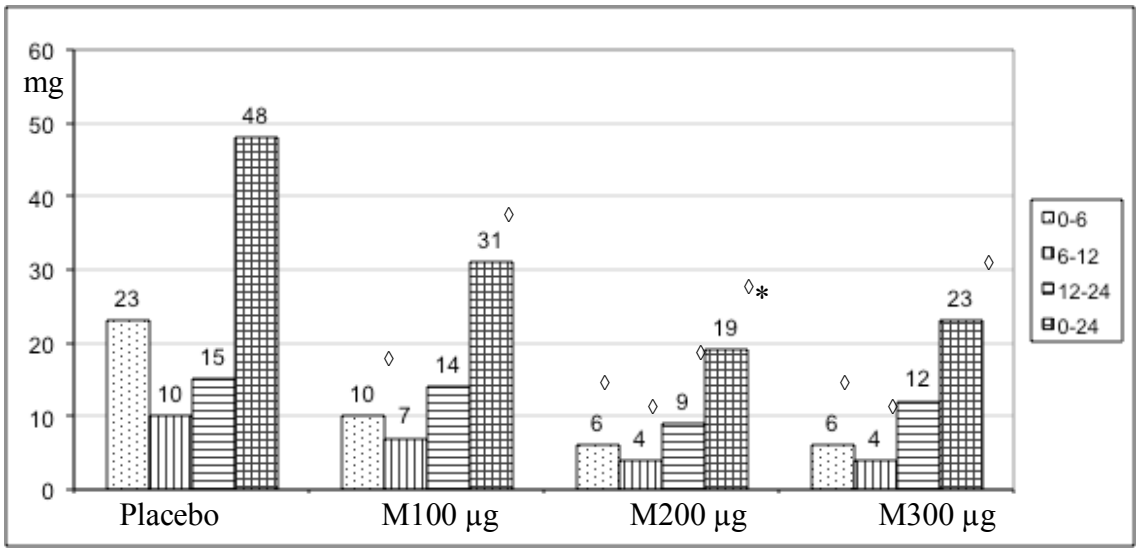
Table 7. Morphine consumption (mg)

		Placebo N = 34	M100µg N = 34	M200µg N = 31	M300µg N = 37
Hour 0-6	Mean ± SD	23 ± 12	10 $^{\lozenge}$ ± 9	6 $^{\lozenge}$ ± 11	6 $^{\lozenge}$ ± 9
	Median[Range]	*21 [6-61]*	*8 $^{\lozenge\lozenge}$ [0-35]*	*2 ** [0-52]*	*2 [0-40]*
Hour 6-12	Mean ± SD	10 ± 8	7 ± 9	4 $^{\lozenge}$ ± 6	4 $^{\lozenge}$ ± 7
	Median[Range]	*8 [0-40]*	*4 $^{\lozenge}$ [0-40]*	*2 [0-24]*	*2 [0-34]*
Hour 12-24	Mean ± SD	15 ± 13	14 ± 11	9 $^{\lozenge}$ ± 8	12 ± 12
	Median[Range]	*12 [2-64]*	*12 [0-42]*	*10 [0-30]*	*10 [0-49]*
Hour 0-24	Mean ± SD	48 ± 27	31 $^{\lozenge}$ ± 25	19 $^{\lozenge}$* ± 19	23 $^{\lozenge}$ ± 24
	Median[Range]	*42 [19-130]*	*22 $^{\lozenge\lozenge}$ [0-81]*	*14 * [0-88]*	*16 [0-116]*

Regarding mean: $^{\lozenge}$Significant difference versus placebo, P=0.05
* Significant difference versus M100, P=0.05

Regarding median: $^{\lozenge}$*Significant difference M100 versus placebo, P=0.05,* $^{\lozenge\lozenge}$ *P=0.01*
* *Significant difference M200 versus M100, P=0.05, ** P=0.01*
No significant difference M300 versus M200

Figure 10. Morphine consumption (mg) as mean



$^{\lozenge}$Significant difference versus placebo, P=0.05
* Significant difference versus M100, P=0.05

Table 8. Adverse events analyses; VAS (pain)

VAS(pain) Postoperative hour	Placebo n =34 or in ( )	M100 µg n = 34 or in ( )	M200 µg n = 31 or in ( )	M300 µg n =37 or in ( )
Rest 1 h	4 [0-9]	3 [0-8]	2 [0-6]	0 [0-7]
Rest 2 h	3 [0-8]	2 [0-7] (33)	1 [0-5]	0 [0-5]
Rest 4 h	3 [0-8]	1 [0-6]	0 [0-5] (30)	0 [0-6]
Rest 6 h	2 [0-4]	1 [0-7]	0 [0-5]	0 [0-4]
Rest 12 h	1 [0-6]	1 [0-6]	0 [0-6]	0 [0-7]
Rest 24 h	1,5 [0-7]	2 [0-6]	1 [0-6]	1 [0-6]
Movement 1 h	4 [0-9] (33)	3 [0-8] (32)	3 [0-6] (28)	1 [0-7] (35)
Movement 2 h	3 [0-7] (33)	3 [0-7] (33)	2 [0-5] (30)	1 [0-7]
Movement 4 h	3 [0-9]	2 [0-7]	1 [0-5] (30)	1 [0-7]
Movement 6 h	3 [0-6]	1 [0-7]	1 [0-5] (30)	1 [0-8]
Movement 12 h	1 [0-6]	1 [0-7]	1 [0-6] (30)	1 [0-8]
Movement 24 h	2 [0-7]	2 [0-6]	2 [0-6] (30)	1 [0-7]

Values are expressed as median with [range] during postoperative recovery 1 - 24 hours.

Table 9. Adverse events analyses

	Placebo N =34	M 100 µg N = 34	M200 µg N = 31	M300 µg N=37
VAS(pain) rest > 4	**22** /5/6/1	**28** /4/1/1	**24** /5/1/1	**30** /5/1/1
VAS(pain)movement > 4	**18** /8/6/2	**26** /4/1/3	**21** /7/2/1	**26** /9/1/1
Itching rescue medication	**34** /0/0	**30** /1/3	**30** /1/0	**32** /4/1
PONV rescue medication	**20** /7/6/1	**18** /7/8/1	**16** /6/3/6	**19** /12/2/4
HR < 45/min	**33** /1	**34** /0	**31** /0	**36** /1
Syst. BP < 90	**33** /0/1	**33** /0/1	**28** /3/0	**32** /4/1
Sedation grade1/ 0-3	**10** /7/5/12	**14** /4/4/13	**11** /2/1/17	**14** /8/0/15
Sedation grade 2-3/ 0-3	**30** /3/0/1	**30** /1/2/1	**27** /3/1/0	**29** /3/1/4
Respiratory rate < 8/min	**30** /4/0/0	**28** /5/0/1	**23** /7/ 0/1	**34** /1/1/1
Respiratory rate >20/min	**33** /1	**32** /2	**29** /2	**35** /2

Values are expressed as number of patients that experience adverse events,
occurring number of times: **0** /1/2/3 or more, during postoperative recovery 1-24 hour.
No significant difference was seen between any morphine group or groups versus placebo.

5.1.3 Study III

Responding clinics: In total, 68% of obstetric anaesthesia units, (32/ 47) responded to the questionnaires, and the sizes of these units correspond to 83% of annual CS in Sweden. Responding frequency was correlated to the size of the unit. We got answers from 90% (19/21) of the units with over 2000 births/year versus only from 50% (13/26) of the units with less than 2000 births/ year. There was 100% response from the 15 units performing more than 400 CS/year.

Caesarean sections (CS)

Table 10 shows the practice of intrathecal opioids in CS. At least one opioid was used as adjunct to local anaesthesia in all responding units.

Intrathecal morphine: In 20 out of 32 units ITM was used routinely in CS spinal anaesthesia. Additional three units commented that they intended to change routines within the next year and start including ITM. The most common ITM dose was 100 μg, used in 17/20 units and three units used 125 μg. Combination of morphine with either fentanyl or sufentanil and bupivacaine was most common, practiced by all units, except for two. One of these units answered that they will start to add fentanyl.
Intrathecal fentanyl was added in CS anaesthesia in 21/32 units; 5 units used exclusively fentanyl, without morphine. The most common dose used was 10–12.5 μg (18 units) and 15–20 μg doses were used in 3 units.
Intrathecal sufentanil supplement was less commonly used in spinal CS anaesthesia; 9/32 units, where sufentanil was added as the sole opioid by seven units. Sufentanil doses were either 2.5 μg (4 units) or 5 μg (4 (units) and in one unit a 5–10 μg dose was used.

In total, the combination morphine/fentanyl was most common, used in 16 units, combination morphine/sufentanil less common, used in 2 units, and solely morphine used in 2 units, solely fentanyl used in 5 units and 7 units used solely sufentanil as supplement to bupivacaine in CS spinal anaesthesia.
One unit that responded routine use of ITM for CS did not include any dose of intrathecal morphine, but only sufentanil and is consequently not included in Table 10 among morphine use and the unit is considered as none user of ITM.

Epidural morphine supplement to CS epidural anaesthesia was less common than ITM in spinal anaesthesia: 12/32 units. The most common epidural dose of morphine, 2 mg was used in 10 units, one unit used 4 mg and one unit used a 1 mg dose of morphine.
Epidural fentanyl was added (50–100 μg) in the epidural for CS anaesthesia in 10 units.
Epidural sufentanil was used in 15 units as the opioid with rapid onset of action in the CS epidural anaesthesia. Doses up to 10 μg were used in 11 units, doses up to 25 μg were administered in 3 units and one unit added a 25–50 μg dose sole sufentanil to local anaesthesia.

Single spinal labour analgesia.

None of the units reported use of morphine in spinal labour analgesia.

Hysterectomy

Intrathecal morphine in spinal anaesthesia was administered in hysterectomy in 20 of the 32 answering units. The dosage was spread, 9 clinics used 200 µg, 5 used 120–140 µg, another 5 used 100 µg and one unit administered 80 µg dose of ITM.

In other gynaecological operations, like other gynaecological abdominal surgery, malign robot surgery and perineoraphies, 7 of 32 clinics used ITM. Epidural morphine was used in one unit, in malign gynaecological surgery.

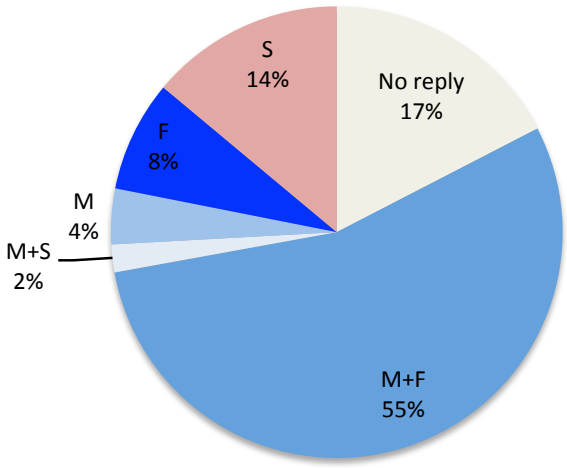
Postoperative monitoring.

The first postoperative 2–6 hours after CS patients were monitored in either the postoperative ward or the obstetrical ward (routinely in eight hospitals and occasionally in some hospitals) and the following hours up to 12 hours patients were usually monitored in the regular ward. Risk of respiratory depression and difficulties to monitor were noted as the main reasons for withholding use of spinal/epidural morphine by seven of the 12 units that did not use it.

Figure 11. The use of intrathecal (left) and epidural (right) opioids as supplement to local anaesthetics in CS in Sweden. Impact of routines is expressed as approximated size of obstetric anaesthesia units, with regard to total performed CS at the units respectively.

M=Morphine, F=Fentanyl, S= Sufentanil

Spinal opioids



Epidural opioids

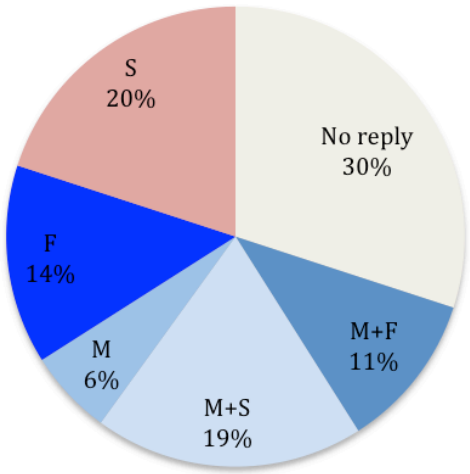


Table 10. The use of opioid supplementation to bupivacaine in CS in different obstetric anaesthesia units. To approximate the size of unit and impact of routine, share of total performed number of CS in responding units and share of CS in Sweden respectively.

Caesarean section			**Units**	Share of total performed CS …	
				…in the responding units	…in Sweden
Responding rate			32/47		*83%*
Intrathecal	Morphine	IT Morphine	20	*73%*	*61%*
		IT Morphine dose 100 /125 µg	17/3		
		IT Morphine + fentanyl	16	*65%*	*55%*
		IT Morphine + sufentanil	2	*3%*	*2%*
		IT morphine but no IT fentanyl / sufentanil	2	*5%*	*4%*
	Fentanyl	IT Fentanyl	21	*75%*	*63%*
		IT fentanyl dose 10–14/ 15-20 µg	18/3		
		IT fentanyl but no IT morphine	5	*10%*	*8%*
	Sufentanil	IT Sufentanil	9	*20%*	*16%*
		IT sufentanil dose 2.5 / 5/ 5-10 µg	4/4/1		
		IT sufentanil but no IT morphine	7	*17%*	*14%*
Epidural	Morphine	EDA morphine dose 1 / 2 / 4 mg	1/10/1	*44%*	*37%*
		EDA Morphine + fentanyl	3	*13%*	*11%*
		EDA Morphine + sufentanil	5	*23%*	*19%*
		EDA morphine but no EDA fentanyl / sufentanil	4	*8%*	*6%*
	Fentanyl	EDA fentanyl 50-100 µg	10	*30%*	*25%*
		EDA fentanyl but no EDA morphine	7	*17%*	*14%*
	Sufentanil	EDA sufentanil 5-10/15-25/25-50 µg	11/3/1	*47%*	*39%*
		EDA sufentanil but no EDA morphine	10	*24%*	*20%*

5.1.4 Study IV

Forty mothers with BMI >30 kg/m^2, scheduled for elective CS in spinal anaesthesia were invited to participate: 27 mothers consented but four of them had contractions causing early acute CS delivery. Among the 23 mothers that were included, 3 polygraphy registrations failed. Thus, 20 mothers were included in analysis.

The mean BMI was 35 ± 4 (30–42), mean age was 35 ± 5 (24–43) years and mean ESS 6 ± 3 (0–12) with 5 mothers scoring an ESS of <5, 12 scoring an ESS between 5 and 10, and 3 had an ESS score >10.

Polygraphic registration: Mean bedtime was 585 minutes (378–818) during the polygraphic registration.

Oxygen saturation: The mean SpO_2 registered was 94% ± 1.3 (91–96%). Four mothers had mean saturation between 91 and 93%, but no had a mean SpO_2 < 91%. The mean nadir saturation was 71% ± 10 (49 – 81%).

AHI was (mean) 6.6 ± 5.2 (0–18.2) "Normal" AHI (<5), was registered in 11 mothers, AHI ≥5 and <15 was registered in 7 mothers, and 2 mothers had an AHI ≥15 and <30. No mother had an AHI ≥30. The mean longest apnoea duration was 30 ± 27 seconds, and mean longest hypopnea duration 55 ± 25 seconds. The 2 mothers with high AHI (15.3 and 18.2) did not correlate with high ODI or hypercapnia on the $TcCO_2$ registration.

ODI was (mean) 4.4 ± 3 (0–10.3). "Normal" ODI <5 was registered in 11 mothers, ODI between 5 and 10 was registered in 8 mothers, and 1 mother had an ODI of 10.3.

$TcCO_2$ was (mean) 4.7 ± 0.3 (4.1–5.2) kPa, and mean of max $TcCO_2$ was 5 ± 0.5 kPa. No mother had $TcCO_2$ >5.9 kPa.

We found no correlation between AHI, ODI, BMI and ESS (Figure 12 -15). The Nox device showed a correlation between AHI and ODI 0.7 with the ODI providing higher indices, the Embletta showed a correlation 0.78 with AHI showing higher indices.

Routine clinical monitoring did not show any clinical signs or symptoms of severe respiratory depression and no mother needed naloxone treatment.

Pain: During the whole postoperative first day and night, eleven patients had maximum NRS 4 at movement once, and another three patients maximum NRS 5. At least one episode of pain at movement, maximum NRS 4-5 was registered in three patients during postoperative hours 0-6 and maximum NRS 8 by one. During the next postoperative hours 6-12, six patients experienced pain NRS 4-5 and two patients 6-7. Between postoperative hours 12-21 seven patients experienced NRS 4-5, one 6-7 and three 8-10 at movement. Rescue pain treatment was administered as buprenorphine 0.2 mg to six mothers, and one mother received 5 mg morphine i.v. 15 h postoperatively; two of those who received rescue pain treatment were unable to use NSAID (Table 11).

Two mothers, experienced nausea, one was administered metoclopramide. Light pruritus, was experienced by 10 patients, and more severe pruritus by two patients and four mothers was treated with clemastine.

The median discharge time was 49 h; eleven mothers were discharged after 44-53 hours, 5 mothers after 71-74 hours, one after 82 hours and one mother with preeclampsia and infection stayed in hospital for 120 hours.

Figure 12-15. Values plotted for each mother, no correlation seen.

Figure 12. AHI (*x*) and ODI (*y*)

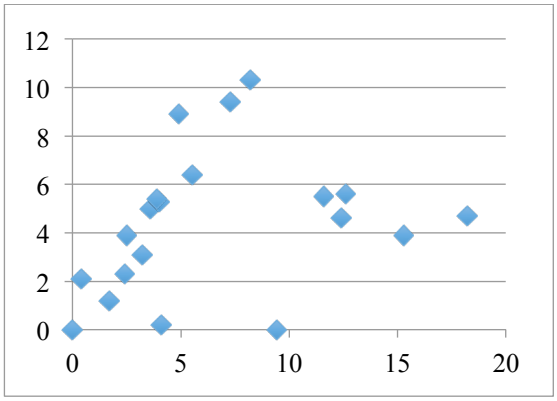


Figure 13. ESS *(x)* and AHI *(y)*

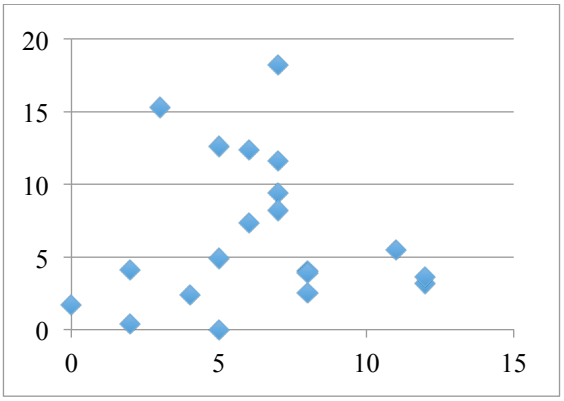


Figure 14. ESS *(x)* and ODI *(y)*

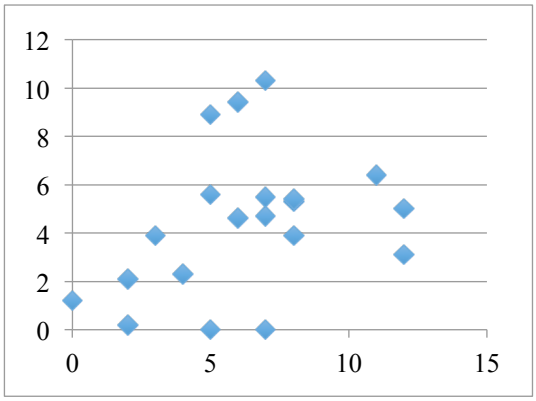


Figure 15. BMI *(x)* and AHI *(y)*

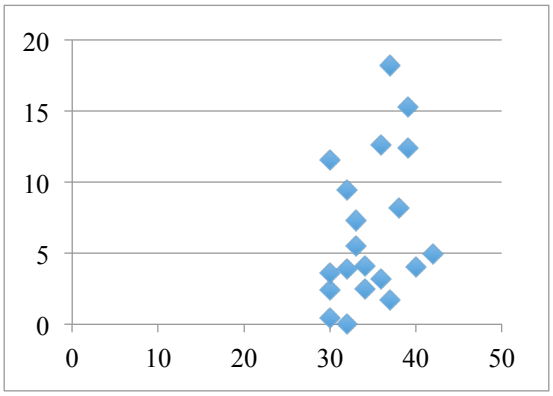


Table 11. Rescue pain medication administered to the patients

Patient no	Ibuprofen 400 mg x 3	Rescue Buprenorfin - Temgesic®		Rescue Morphine i.v.
6	No	0.2 mg	6 h + 10 h postop.	
7	Yes	0.4 mg	6 h + 12 h postop.	
9	Yes	0.2 mg	6 h + 15 h postop.	
10	Yes	0.4 mg	3 h+9 h+21 h postop.	
11	Yes			5 mg 15 h postop.
14	Yes	0.2 mg		
18	No	0.4 mg	3 h + 18 h postop.	

5.1.5 Study V

From 1st of January to October 31st 2016 we identified 150 ECS from the record systems but data was only possible to retrieve for 135 cases that were included in analysis.

For all the 135 ECS the DDI (median) was 17 minutes (range, 5–41). With GA the DDI (median) was 10 -13 min shorter compared to SA (DDI 20 min) and tEDA (DDI 23 min) respectively ($p<0.0005$; Table 12). The time to establish adequate anaesthesia accounted for the major time difference. The time from anaesthesia start to ready for surgery was shortened by 7 and 8 minutes with GA (2 min. range 1-8 min) as compared to SA (9 min, range 1-16) and tEDA, 10 min, range 1-23) respectively. Thus the time difference between SA and tEDA was 1 min. Different working shifts: daytime, on call during the week and weekends did not affect DDI or the separated time events like call to start of anaesthesia, start of anaesthesia to surgery, and surgery to delivery. No significant difference was observed (Table 13, Figure 16).

Apgar score of <7 at 5 minutes were registered in 14 neonates: 11/64 neonates with mothers having GA, 2/30 that received SA and 1/42 that received tEDA ($p < 0.05$). pH < 7.1 were registered in 17 neonates: 14/64 neonates with mothers receiving GA, 2 /30 mothers receiving SA (DDI 15 and 17 minutes), and 1/41 mothers receiving tEDA (DDI 24 minutes). Observation and treatment in neonatal intensive care was provided for 39 neonates: 22, 10 and 7 that had GA, SA and tEDA, respectively (ns; Table 14 and 15).

Table 12. Time events for different anaesthetic techniques

	Call - Start Anaesthesia	**Start Anaesthesia – Ready for Surgery**	**Surgery - Delivery**	**DDI**
GA (n = 64)	6 (1–17)	2 (1–8)	2 (1–4)	10 (5–21)***
SA (n = 30)	8 (1–23)	9 (1–16)	3 (1–7)	20 (13–33) ns.
EDA (n = 41)	8 (1–25)	10 (1–23)	3 (1–8)	23 (12–41) ns.
ALL (n =135)	6 (1–25)	5 (1–23)	2 (1–8)	17 (5–41)

Data are presented in minutes as median (range)

*** $P < 0.0005$ vs. regional anaesthesia, ns. No significant difference between SA and tEDA

GA general anaesthesia, SA Spinal anaesthesia, tEDA top up Epidural anaesthesia, DDI Decision to delivery interval

Table 13.Time events for the different work shifts: day time, on call during the week and at weekends.

		Call - Start Anaesthesia	Start Anaesthesia – Ready for surgery	Surgery - Delivery	DDI
Daytime	(n = 37)	6 (1–25)	7 (1–23)	3 (1–6)	21 (6–41)
On-call	(n = 60)	6 (1–23)	4 (1–19)	2 (1–7)	14.5 (6–36)
Weekend	(n = 38)	9 (1–17)	6 (1–17)	2 (1–8)	18 (5–39)
All	*(n = 135)*	*6 (1–25)*	*5 (1–23)*	*2 (1–8)*	*17 (5–41)*

Data are presented in minutes as median (range)

Figure 16. DDI for ECS studied (n=135) in relation to time of day

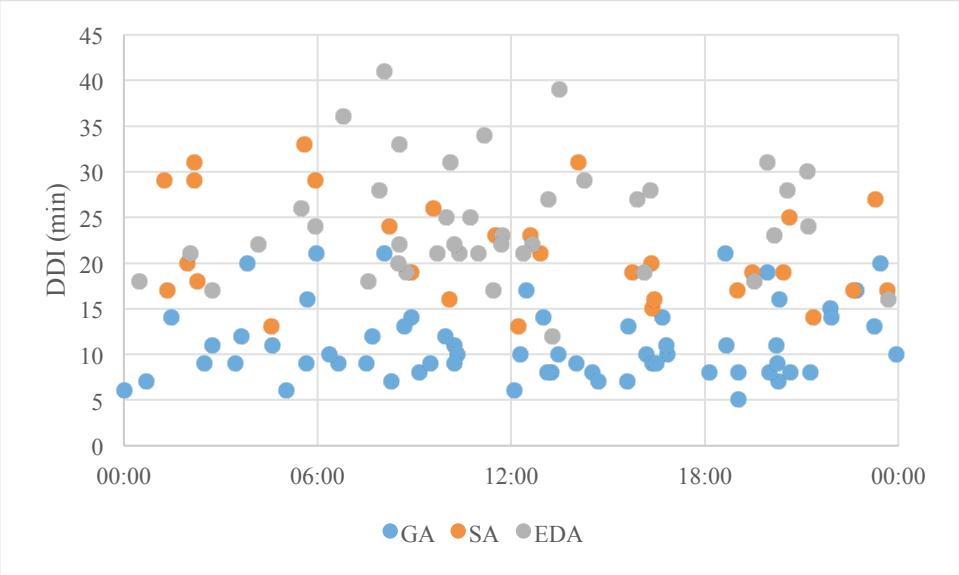


Table 14. Comparison of anaesthetic technique and neonatal outcome.

Type of anaesthesia	**GA** (n = 64)	**SA** (n = 30)	**EDA** (n = 41)
Apgar score at 5 min, median (IQR)	9 (3)	10 (2)	10 (1)
Apgar score at 5 min. < 7, n (%)	11 (17) *	2 (7)	1 (2)
Umbilical cord Arterial, mean**:**			
pH	*7.13*	*7.21*	*7.23*
pCO_2	*9.07*	*7.40*	*7.28*
Base Excess	*-9.53*	*-6.56*	*-6.55*
CPAP, n (%)	31 (48)	12 (40)	13 (31)
Ventilation, n (%)	26 (40)	13 (43)	6 (14)
Intubation, n (%)	5 (8)	1 (3)	1 (2)
Neonatal unit, n (%)	22 (34) ns	10 (33)	7 (17)

* $p<0.05$ Chi-square test, ns none significant between anaesthetic techniques

Table 15. CS indications, type of anaesthesia and neonatal pH at birth < 7.1

CS Indication	**GA** n=64		**SA** n=30		**EDA** n=41	
	number	*n pH<7.1*	number	*n pH<7.1*	number	*n pH<7.1*
Foetal distress	36	*7*	16	*1 (DDI 15)*	32	*1 (DDI 24)*
Foetal distress+ placental abruption					1	
Foetal distress+ breech presentation					1	
Foetal distress+ uterine rupture	1					
Foetal distress+ placental abruption+ uterine rupture	1	*1*				
Foetal distress+ delivery of twins	1					
Foetal distress+ cord prolapse	1					
Foetal distress + IUGR			1			
Placental abruption	9	*2*	4	*1 (DDI 17)*		
Breech presentation	1		4		1	
Uterine rupture	1	*1*				
Failed vacuum assisted delivery	7	*2*	5		5	
Cord prolapse	6	*1*				
Delivery of twins					1	

GA general anaesthesia, SA spinal anaesthesia, EDA epidural anaesthesia, DDI decision – delivery time in minutes

Three SA-CS had DDI longer than 30 minutes, with additional 1-3 minutes, and the neonatal outcome was for all three cases 10 for Apgar at 5 min. and pH*a* 7.21-7.29.
Seven tEDA-CS had DDI longer than 30 minutes, with additional 1-11 minutes, with the neonatal outcome for Apgar at 5 min. 9 for one, and 10 for the other six, and median pH*a* 7.22 within range 7.13-7.29.

5.2 TABLES - REFERENCES OF INTRATHECAL ANAESTHESIA IN LABOUR AND ABDOMINAL HYSTERECTOMY

In order to put study I and II in perspective I have listed them with references, including methods, different doses used and most important results in table 16 – labour analgesia and 17 – abdominal hysterectomy for overview.

5.2.1 Table 16. References listed for labour spinal analgesia

SA spinal analgesia, EDA epidural, CSE combined spinal epidural
M morphine, F fentanyl, S sufentanil, B bupivacaine, diff d different doses, vs. versus

Reference	Method Labour analgesia	ITM µg *(n)*	ITother opioid µg *(n)*	IT local anaesthetics and other	Results
Scott PV et al. (32) 1980	SA M	**1500** *(12)*	No	No	1st stage No pain/ 2nd stage 4 pt no pain+3 pt less pain. Itching (face), nausea and vomiting, frontal headache; CS: 3pt, Forceps: 3pt
Baraka A et al. (33) 1981	SA M diff. d.	I **1000** *(7)* II**2000** *(13)*	No	No	Onset: 15 -60 min; Duration: 8-11 h Majority: Somnolence, nausea, vomiting, itching
Abboud TK et al. (6) 1984	SA M diff. d.	I **500** *(12)* II **1000** *(18)*	No	No	93%: at least 50% pain relief. Onset: 15-60 min after inj. Duration: 6-8 h 80% pruritus, 53%, nausea or vomiting, or both; 43%, urinary ret. 43% drowsiness
Leighton BL et al. (58) 1989	SA MF	**250** *(15)*	Fentanyl 25	No	Onset: 5 min after injection Duration (n): Comfortable: (9): Spontaneous labour: 187±148(6) + Oxytocin ind.: 222±196 (3) EDA required (6): Spontaneous labour: 145(1) + Oxytocin ind: 139±57 (5)
Abouleish E et al.(59) 1991	SA M vs EDA B vs CSE MB	I **200** *(20)* II 0 *(22)* III **200** *(20)*	No	I 0 II & III EDA 0.125% 10ml Bupivacaine	Neither ITM 0.2 mg nor 10 ml 0.125% epidural bupivacaine produced effective adequate pain relief in labour, CSE MB produced excellent analgesia. ITM sign. reduced the dosage requirement of epidural bupivacaine. Nausea, vomiting, and pruritus were sign. greater in M groups
Grieco et al. (60) 1993	SA S vs S+ Epinephrine vs MS	III **250**	I & II & III Sufentanil 10	No local anesthesia but II Epinephrine 250µg	Onset: 5 min after injection similar in all groups Duration(n): I(12) 115 ±40 / II(13) 132 ±45 / III(14)135 ±37 Most significant side effects was seen in morphine group – pruritus and nausea Bloodpressure decreased 5 min after it inj. – no diff. btw groups
Herpolsheimer A (61) 1994	SA MF vs controls	I **250** *(75)* II 0	I Fentanyl 25 II 0	No	SA: a satisfactory level of pain relief without disrupting the normal course of labour pruritus (81.3%), urinary reten. (53.3%), nausea and vomiting (44.0%). Headaches (9.3%), respiratory depr (1.3%) oversedation (1.3%)
Campbell DC et al. (62) 1995	SA B vs S vs SB	No	I 0 *(14)* II & III Sufentanil II 10 *(14)* III 10 *(15)*	I Bupivacaine 2.5mg II 0 III Bupivacaine 2.5mg	I Duration: 70 ± 34 min, VAS: More than II & III II Duration:114± 26 min, VAS: More than III beyond 75 min III Duration:148 ± 27 min, VAS: Lowest; Sign. prolonged labour analgesia without adverse maternal or foetal effects. Hypotension: not in the S gr; occurred transiently in the two bupivacaine groups (P < 0.09).
Viscomi CM et al. (63) 1997	SA SB Early vs advanced Labour	No	I & II Sufentanil 10	I & II Bupivacaine 2.5mg	Duration: I cx 3-5 cm *(18)*: 163 ± 57 min ; II cx 7-10 cm *(23)*: 120 ± 26 min p<0.01 cervical dilation and stage of labour significantly impact the effective duration
Asokumar B et al. (64) 1998	SA F vs B vs FB	No	I & III Fentanyl 25 II 0	I 0 II & III Bupivacaine 2.5mg	Duration: I-F 62.5, II-B 55.0, III-F+B 94.5 min, longest in F+B group and a more rapid onset compared with either drug alone.
Palmer CM et al. (65) 1999	SA F diff. d. 7 groups *n=12 in each group*	No	Fentanyl I 5 II 10 III 15 IV 20 V 25 VI 35 VII 45	No	Rapid, profound labour analgesia with minimal side effects. Duration: increased to 89 min with increasing dose up to 25 µg. There is little benefit of increasing the dose beyond 25 µg. No diff. among groups regarding pruritus. Nausea and vomiting were uncommon. FHR did not change after inj.

Reference	Method	ITM	ITother o.	IT la/other	Results
Norris MC et al. (5) 1998	SA S diff. d.	No	I & II Sufentanil I 5 *(32)* II 10 *(31)*	No	I & II: Adequate analgesia. 10µg sufentanil: slightly more profound analgesia, Duration: no diff. between the groups. I & II: significant increases in itching and end-tidal CO2; 10µg dose: more sedation and decrease in SaO2.
Gautier PE et al. (66) 1998	SA S vs 2S vs C vs 2C vs SC vs 2SC *(98)*	No	I+V Sufentanil 2.5 II+IV Sufentanil 5	III+V Clonidine 15 µg IV+VI Clonidine 30 µg	Group Voch VI (Sufentanil 2.5 µg+Clonidine 30 µg) and (Sufentanil 5 µg+ Clonidine 30 µg) had longer duration 145±36 /±45 vs 104 ±35 for sufentanil alone. No adverse events registered.
Palmer CM et al. (65) 1999	SA F vs FB vs F2B B diff. d.	No	I & II & III Fentanyl 25	I 0 II & III Bupivacaine II 1.25 mg III 2.5 mg	I (30) Duration: 92 ± 23 min II (30) Onset: faster; Duration 94 ± 25 min III (30) Onset : Fastest; Duration 108 ± 20 min was longer No differences btw groups in pruritus or bloodpressure
Sia AT et al. (55) 1999	SA 2S2B vs SB diff. d. of S and B	No	I Sufentanil 10 II Sufentanil 5	I Bupivacaine 2.5 mg II Bupivacaine 1.25 mg	I lasted longer than II I: had lower VAS for the first 5 min ($P < 0.05$) and a higher level of sensory blockade (median of T4 compared with T7 in II; $P < 0.01$) hypotension I - 9 pt vs II - 2 ;$P < 0.05$, a greater degree of motor block ($P < 0.05$), and a higher incidence of sedation I - 9pt vs II -1; $P < 0.01$.
Cheng CJ et al. (67) 2001	SA SB vs FB	No	I Sufentanil 5 II Fentanyl 25	I & II Bupivacaine 1.25 mg	No significant difference in the duration: I 118 ± 54 min vs II 109 ± 49 min Group II had a more rapid onset ($P<0.05$) and a higher cephalad block (median T4 *vs* T7, first 30 min after the block.
Yeh HM et al. (34) 2001	SA FB vs MFB	I 0 II **150**	I & II Fentanyl 25	I & II Bupivacaine 2.5 mg	Duration (n): I FB (48) - 148 ± 44 min vs II MFB (47) - 252 ± 63 min $p<0.05$ Adverse effects: no sign. Differences
Eriksson SL et al. (68) 2003	SA SB	No	Sufentanil 7.5 *(40)*	Bupivacaine 2.0 mg	Onset & duration: VAS at 5, 15, 30, 60, 90, 120 and 150 min were 1.5, 0.5, 0, 1, 1.5, 2 and 3 respectively. 77% scored analgesic quality as excellent. Hypotension: 6 pt, FHR -disturbances 4 pt, Motor block, sedation and nausea were rare. Pruritus: 85%
Hess PE et al. (69) 2003	SA FB vs MFB	I **0** II **125**	I & II Fentanyl 12.5	I & II Bupivacaine 2.0 mg	Duration: similar between groups (89 min vs 84 min: only 20% of MBF experienced prolonged analgesia. During subsequent epidural analgesia, MBF had sign. lesser rate of breakthrough pain
Viitanen H et al. (70) 2005	SA FB	No	Fentanyl 25 *(209)*	Bupivacaine 2.5mg	Duration: 101 ±34 min; Pain relief: excellent - 65%, moderate -20%, inadequate - 14%, 26% pt got additional analgesia (18% - VAS >3 at 20 min after spinal inj. and 8% - spinal block wore off before delivery)
Vasudevan A et al. (71) 2007	SA FB vs MFB	I **0** II **100**	I & II Fentanyl 12.5	I & II Bupivacaine 2.0 mg	MFB had a significantly lower rate of breakthrough pain than the FB group [0.6 (0.6) vs 1.1 (0.8) episodes per pt; $P<0.01$] and longer time to first episode of breakthrough pain (300 vs 180 min)
Kuczkowski K et al. (72) 2008	SA BMC No compare	250 *(62)*	0	Bupivacaine 2.5 mg Clonidine 45 µg	Maternal satisfaction 81% very satisfied +11% satisfied. Mean painVAS 30min-3 h: 3.3-3.9, 4h-12h: 4.1-5.9; Nausea 9.6%, occasional shivering, 6.5%, pruritus, 8%. No respiratory depression, hypotension or foetal complications.
Hein A et al. study I 2010	SA SB vs MSB M diff. d.	I **0** II **50** III **100**	I & II & III Sufentanil 5	I & II & III Bupivacaine 1.25 mg	Duration: similar between groups, no sign differences regarding onset, or side effects.
Anabah T et al. (73) 2015	SA MFB No compare	200 *(328)*	Fentanyl 25	Bupivacaine 2.5 mg	98.8% mild-no pain, 1.2% moderate pain; 87.7% no effect on ambulation, 12.3% mild effect; 31.3% pruritus, 26.8% nausea, 3.9% both pruritus + nausea; 14.5% required naloxone treat pruritus/nausea or both; 3.6% foetal bradycardia

5.2.2 Table 17 References listed for intrathecal anaesthesia for abdominal hysterectomy

Reference	Method	ITM µg/ µg/kg	Intrathecal other drug	And GA	Vs. GA	Results
Yamaguchi H et al.(74) 1989	SA tetracain + M diff. d	0 / 30 / 40 / 60 / 80 /100	hb tetracaine 12-14 mg	No	No	SA: 40-80 µg M + tetracaine made po iv narcotics unnecessary in 60-70% for 24 h and minimal adverse effects
Sarma VJ et al. (9) 1993	GA vs GA+ Postop SA M diff d	0 / 100 / 300 / 500	0	GA-inhal.	GA-inhal.	SA: M 0.1, 0.3, 0.5: Lower VAS vs. GA; M 0.3 & 0.5 at 10 h- lower VAS vs. 0.1; VAS: No diff 0.3 – 0.5 Nausea & vomiting most in GA, lowest in 0.3; Pruritus most in M-groups, most in 0.5
Karaman S et al. (75) 2006	GA vs GA+ SA M	5 µg/kg	0	GA-inhal.	GA-inhal.	SA: Lower(sign) VAS po, Less PCA M-consumption, lower stressresponse
Vaida SJ et al. (56) 2000	GA vs GA+ SA B	No	12 mg hb bupivacaine	GA-inhal.	GA-inhal.	SA: Lower VAS 2 h po Similar VAS 4-24 h po Less PCA M-consumption
Wang JJ et al. (8) 1996	GA vs SA B	No	15 mg hb bupivacaine	No	GA-inhal.	SA: Lower VASrest 6-24 h po Lower VAScough 6-30 h po Less M-consumption 0-24 h
Massicotte L et al. (76) 2009	GA vs SA + sed MFB	150	15 mg hb bupivacaine + fentanyl 15 µg	No	GA-inhal.	SA: Lower VASrest -18 h po, Lower VASstress-48 h; Less PCA M-consumption. Shorter PACU & hospital stay
Sprung J et al. (77) 2006	SA vs GA	2 µg/kg, max 200 µg	15 mg hb bupivacaine + clonidine 1 µg/kg	No	GA-inhal.	SA: Lower VAS 0-14 h SA: Lower pain 2 weeks po No differences SA vs. GA at 12 weeks
Kroon UB et al. (78) 2010	SA + TIVA vs GA	100	15 mg hb bupivacaine	GA-TIVA	GA-inhal.	SA+ TIVA: shorter po ward 180 vs 237 min, shorter hospital stay 2 vs 3 days, less nausea
Borendal Wodlin N et al. (79) 2011	SA + sed. vs GA	200 µg	20 mg hb bupivacaine	No	GA-TIVA	SA: Less M-consumption 0-24 h, faster recovery of bowel function. SA groups: more Pruritus and vomiting
Hein A et al. study II 2012	SA + GA M diff d	0 / 100 / 200 / 300	12 mg hb bupivacaine	GA inhal.		SA: M groups: less total iv M-consumption 0-24 h po, least in 200 µg. Lower VASrest 0-12 h po Pruritus only in ITM-groups. Emesis similar in all groups

SA spinal analgesia, GA general anaesthesia, GA inhal. general anaesthesia inhalational, TIVA total intraveno,us anaesthesia, sed. sedation, vs versus, M morphine, F fentanyl, B bupivacaine, hb hyperbaric, IT intrathecal, iv intravenous, po postoperative, diff d. different doses, PCA patient control analgesia, PACU postanaesthesia care unit

6 DISCUSSION

6.1 STUDY I AND II

This thesis has its focus on pain management in the female patient, pain associated with childbirth, CS or hysterectomy. We studied the effects of addition of different low doses of ITM to fixed doses of local anaesthesia and in the first study a fixed dose of fast acting opioid as well. We studied analgesia for different mechanism of pain; in study I – during labour with primary outcome duration of analgesia and study II – post abdominal hysterectomy pain, with primary outcome need of additional analgesics. In study I we did not find any clinically relevant effect of adding 50 or 100 μg of ITM for analgesia in established labour with regard to lengths of analgesia. In study II however we found addition of ITM associated with reduced accumulated 24 hours post-operative morphine consumption in all three morphine groups 100, 200 and 300 μg and the opioid sparing effect seemed to plateau at 200 μg. Patients receiving ITM scored lower VAS pain at rest postoperatively the first 12 hours, but no difference regarding number of patients with VAS pain > 4 was seen.

6.1.1 Power analyses

We believe the studies were correctly powered. In our placebo group regarding study I the duration of effective analgesia (60-240 min) was in line with what we expected from other studies using similar doses of bupivacaine and sufentanil (55, 67). The placebo morphine consumption in study II was in the same magnitude with what was anticipated in the power-analysis (8).

6.1.2 Patient demographics and basal data influencing experienced pain

In both studies we were aiming for homogenous groups regarding severity of pain. Regarding study I we selected nulliparous women with a cervical dilatation at recruitment of 3-7 cm. Cervical dilatation is known to influence grade of pain and the chosen range may be wide (63). However no differences regarding onset time and duration were detected when directly comparing women with an initial dilatation of either 3-5 or 6-7 cm. Regarding study II we registered operation time, blood loss and type of tumours and find the groups comparable.

6.1.3 Pain-rating

We defined experienced pain as VAS > 4. One might argue that this is high but it was at the time in accordance with the routines of our departments. It is unlikely to have affected any potential difference on duration of analgesia or the morphine consumption respectively between the study groups. Pain at rest was overall well controlled in both studies.

6.2 INTRATHECAL MORPHINE IN LABOUR

In labour, epidural analgesia is shown to give the most effective pain relief (4). Spinal labour analgesia with varying mixture of local anaesthetics and different opioids has shown to produce effective labour analgesia, with the advantages of being easier, faster and of less cost

to administer but with limitation of restricted duration (80). When pencil point shaped needles of small sizes are used and small volumes of drugs are injected the risk of complication with spinal labour analgesia seems even less than with labour epidurals. Morphine in doses 0.25 – 2 mg has previously been shown to produce excellent labour analgesia but with high frequency of side effects (Table 16)(6, 33, 61). Yeh et al. found a combination of bupivacaine 2.5 mg, fentanyl 25 µg and low dose of morphine, 150 µg ITM to reach duration of 252 min. vs. 148 min. without ITM, and observed no difference regarding side effects (34). This is a notable extension of the duration of clinical value. Our aim was to study if reduced dose of ITM in a spinal mixture would prolong duration of labour analgesia. In CS anaesthesia low doses have been proven efficient for postoperative pain relief (38). We used a low dose basic regime for all groups, 1.25 mg bupivacaine + sufentanil 5 µg, with a previously shown shorter duration (120 min) than with doubled doses (164 min) but also less adverse effects (55). Still we believe this mixture lasted long enough, 60 – 240 minutes in our placebo group, for the onset of ITM component, since peak analgesic effect for ITM is reached within 30-60 minutes (34, 81). The patients had an epidural catheter to use on demand (administered by the midwife) when pain returned after spinal analgesia waned. Apart from duration of analgesia, we analysed mean hourly consumption of epidural bupivacaine and sufentanil and found no differences between the groups. This indicates that there neither was a more prolonged analgesic effect of the addition of morphine in our study. As table 16 shows there are only, two other to us known studies, exploring effects of ITM in doses of less than 150 µg. In accordance to our study addition of 125 µg ITM to bupivacaine 2 mg and fentanyl 12.5 µg did not prolong the duration of spinal labour analgesia, but Hess et al. observed reduction in breakthrough pain during continued labour and less need for analgesia first 24 hours after delivery (69). This is in line with observations of Vasudevan et al. who used the same basal mixture but with supplementation of 100 µg of ITM in a CSE with immediate start of continuous epidural infusion of bupivacaine/fentanyl after spinal injection (69, 71). However we did not follow our patients regarding breakthrough pain during continued labour after spinal duration had waned off, or the amount of consumed rescue analgesia after delivery, which is a weakness in our study. Severe, acute pain after vaginal delivery has been found in 1 of 13 women, and is the most important risk factor for developing persistent pain after childbirth (18). Mac Arthur et al. administered 2.5 mg of epidural morphine after vaginal delivery before labour epidural catheter was removed and found a 78% reduction in analgesic requirements (82). However we are not able to say whether addition of 50 or 100 µg ITM affected acute pain after vaginal delivery, or in a longer perspective, persistent pain weeks after delivery, but this is an interesting aspect for future studies.

In study III we found ITM for single spinal labour analgesia was not practiced in Sweden. This is not surprising since in Sweden there are good opportunities, for mothers that request pain relief during delivery, to get an epidural in every delivery department. Epidural analgesia is provided to 35 % among all deliveries in Sweden and 52 % among nulliparous women (54). Single spinal analgesia with opioid mixture recommended, bupivacaine 1.5-2 mg and

sufentanil 5 µg, is used to a much lesser extent, primarily to women when there is a fast progression and delivery is expected soon, within 60-90 minutes. Another indication for spinal analgesia may be when a woman is in so much pain that she cannot cooperate during the procedure of epidural administration, but this can be offered after first pain relief is conducted with a single spinal. Epidural analgesia is more expensive, time and resource consuming, but with the advantage of no restriction regarding duration. In addition, it has the possibility to use in case of caesarean section even in the emergent cases as shown in study V. However in low income, developing countries there are restricted opportunities to offer pain relief to delivering mothers at all. Still management of labour pain is regarded as a fundamental human right by WHO (83). There are reports from Indonesia and Ghana where single spinal analgesia has been used in this context (Table 16)(72, 73). Bupivacaine 2.5 mg is used as basic local anaesthetic in both studies, Kuczkowski et al. added Clonidine 45 µg and 250 µg of morphine and Anabah et al. used Fentanyl 25 µg and 200 µg of ITM as supplement to bupivacaine (72, 73). Both report sufficient pain relief to a large extent, maternal satisfaction rated very satisfied or satisfied in 92% and mild or no pain in 98.8% respectively. Information about duration was not shown in hours or minutes but Kuczkowski et al. reported reduced VAS pain <6, even after 12 hours (Table 16)(72). Clonidine has been described associated with high incidence of maternal hypotension, sedation and foetal heart rate abnormalities (84, 85). However Kuczkowski et al. found no serious advert events and reported low incidences of side effects, pruritus 8% and nausea 9.6% (72). Higher incidences of side effects was found by Anabah et al.; foetal bradycardia was seen in 3.6%, treatment with naloxone was needed in 14.5% for pruritus/ nausea or both (73). In the context of low income country, choosing between pain relief with longer duration and side effects women probably prefer less pain in accordance with mothers rating of side effects observed for caesarean sections (86). Carvalho et al. found pain during and after CS highest ranked of avoidable outcomes followed by vomiting, nausea, cramping and itching (86). Side effects of ITM supplementation during labour analgesia are hard to separate from the side effects from included lipid soluble (“fast”) opioids like pruritus, and experienced effects from delivery, like nausea and vomiting. As long as serious side effects like FHR abnormalities and maternal respiratory depression and hypotension can be avoided and carefully observed and treated, addition of a morphine dose of 150-200 µg seems reasonable (80, 87).

6.3 INTRATHECAL MORPHINE IN ABDOMINAL HYSTERECTOMY

The role of good pain relief both in the acute postoperative period, to enhance a fast recovery process, but also in a longer perspective, in order to reduce persistent postoperative pain and anxiety, is today rather well established (13, 88, 89). However the routines, how to gain good targeted pain relief, vary and are under discussion, but to aim for opioid sparing and use a multi model and individualized approach is not controversial even though not always implemented (90). Fast mobilisation to avoid thrombosis, lung secret problems and bowel problems with constipation and pain from paralytic ileus requires a pain free or low pain-situation (91). Spinal anaesthesia has been used, in order to minimise postoperative pain and

morphine consumption in this concept with different approaches; after or more often before surgery, different drugs and doses, aiming for a mixture with minimal side effects and still long duration of effective pain relief (Table 17)(9, 56, 75-77, 91). Sarma et al. and Karaman et al. compared general anaesthesia with general anaesthesia together with sole spinal morphine anaesthesia (9, 75). Vaida et al. and Wang et al. provided bupivacaine spinal anaesthesia to one group and compared with general anaesthesia, given to both groups and the other group respectively (8, 56). Massicotte et al., Sprung et al., Kroon et al. and Borendahl-Wodlin et al. administered a mixture of spinal bupivacaine 15-20 mg and ITM; 100-200 µg and fentanyl for one study (Massicotte et al.) and clonidine for another (Sprung et al.) study (76-79). The spinal groups were sedated or in the study by Kroon et al. they had TIVA and were compared to general inhalational anaesthesia. Most of the studies assessed postoperative morphine consumption, which was found reduced for SA-groups and /or VAS pain, which also was found reduced. Earlier studies assessed for shorter perspective; first 24 postoperative hours, while studies comparing spinal anaesthesia versus general anaesthesia performed later years have a more protracted and broader perspective, also evaluating start of per oral fluid, removal of indwelling catheter, bowel function, and length of hospital stay. We only followed the patients the first 24 postoperative hours and did not apply a broader view of postoperative recover, nor did we explore occurrence of persistent pain, which is a limitation.

We aimed to explore if one of the three commonly used doses of ITM; 100, 200 or 300 µg was more beneficial than the others, weighing benefits-risks. Our findings imply that there are less postoperative morphine consumption and pain with supplementation of any of these doses morphine, but no extra benefit in doses higher than 200 µg of ITM. First postoperative hours results of morphine consumption and pain rating may have been influenced by the injection of intravenous morphine, given to all patients before extubation, to ensure sufficient pain relief in all groups. We did not include a lipophilic opioid, e.g. fentanyl 10-20 µg or sufentanil 2.5-5 µg as is recommended in CS spinal anaesthesia and as for hysterectomy spinals, is established routine in our department at present, but we did not want another opioid to interfere with our findings about ITM (92). For CS spinal anaesthesia, patients are awake and have increased risk of experiencing pain, nausea and/ or vomiting without fentanyl supplementation intraoperative, but no meaningful postoperative analgesia is found with doses commonly recommended (92-94). All our patients had spinal anaesthesia and general anaesthesia with increasing doses of morphine as the only varying factor.

When comparing side effects we found no serious adverse events, pruritus was only occurring in morphine groups, nausea was not uncommon, but without differences between groups. Sevoflurane nitrous oxide general anaesthesia was used in all groups and may have influenced this; more nausea was found in general anaesthesia group compared with spinal morphine anaesthesia group by Kroon et al. (78). In opposite to those findings Borendahl-Wodlin et al. found more vomiting day of surgery in spinal anaesthesia group having 20 mg bupivacaine with 200 µg morphine complemented with propofol-sedation (79).

Our patients got paracetamol regularly but no NSAID, which has been shown to decrease additional morphine requirements in abdominal surgery and is strongly recommended together with paracetamol on regular basis (95, 96). NSAID were excluded from our protocol since sensitivity is not uncommon and might have been unequally distributed among the groups and thereby interfering with results. Preemptive administration of gabapentin has become popular, in order to prevent neuropathic pain, as it antagonizes N-methyl-d-aspartate receptor (97). Alayed et al. found in their review gabapentin to decrease postoperative pain scores, narcotic consumption, nausea, and vomiting but they excluded studies in which local or regional anaesthesia was performed (97). Kiatchai et al. concluded that a preoperative dose of pregabalin 150 mg, antagonising NMDA receptor, did not affect pain score or morphine consumption when abdominal hysterectomy was performed in spinal anaesthesia with hyperbaric bupivacaine and 200 µg morphine (98).

Spinal anaesthesia including local anaesthetic and ITM in dose range of 200 µg is recommended in open general gynaecologic surgery in a multimodal and opiate sparing strategy in the guidelines for gynaecologic surgery by Enhanced Recovery After Surgery (ERAS®) Society (96). Nelson et al. list benefits like reduced pain and morphine consumption, reduced risk of post-operative ileus, peri-operative stress hormone release and improved recovery with less drowsiness, but with the expense of more pruritus (96). Spinal anaesthesia with 20 mg hyperbaric bupivacaine and 200 µg morphine and propofol sedation was also found more cost-effective than general anaesthesia in abdominal hysterectomy by Borendal Wodlin et al.(99).

In study III we find 20/32 answering units using spinal with addition of ITM for gynaecological operations, mainly hysterectomies, with a variety of dosing spread between 80 and 200 µg, 9/20 using 200 µg dose.

TAP-block is recommended as an alternative if spinal or thoracic epidural is not performed (96). In CS it has been concluded TAP-block is associated with greater postoperative morphine consumption and higher pain scores than ITM but fewer side- effects (100). We find, in agreement with the writer, TAP-block a reasonable alternative when ITM is not used in open gynaecological or obstetric surgery, like after sole general anaesthesia or when contraindicated or as rescue if pain relief provided by ITM is insufficient (96, 100). Addition of dexamethason 8 mg to 20 ml bupivacaine 0.25% for TAP prolonged duration of analgesia and reduced morphine requirements 48 postoperative h. after abdominal hysterectomy performed in general isoflurane anaesthesia, in a study by Ammar et al. with lower incidence of nausea and vomiting (101).

Different surgery methods/approaches have impact on following pain and pain treatment (102). Laparoscopic surgery and robot assisted laparoscopic surgery is increasing and little is known about whether these patients gain benefits from ITM and if so what doses should we use? From laparoscopic colon surgery, pre induction spinal, with a mixture of bupivacaine and diamorphine is known to reduce the stress response and post-operative morphine consumption compared with morphine-PCA based post-operative analgesia

(103). Koning et al. investigated the role of spinal with ITM 240-300 μg depending on age and bupivacaine 12.5 mg in laparoscopic colon surgery within an ERAS program, and their findings about ITM spinal, providing faster and less painful recovery, is just recently published (104). Segal et al. studied robotic gynaecologic surgery; sacrocervicopexy with subtotal hysterectomy, and found general and spinal anaesthesia providing significantly lower pain score, less analgesic use and increased patient and nursing staff satisfaction compared with general anaesthesia alone (105). The intrathecal injection included fentanyl 15 μg and morphine 0.15–0.5 mg, 3 μg/kg, a rather high morphine dose with regards to our findings, with no further benefits with ITM more than 200 μg (105). Arguments in favour of spinals with ITM, compared with thoracic epidurals**,** are easier handling, easier and earlier mobilizing and shorter hospital stay (103).

6.4 NEUROAXIAL MORPHINE IN CAESAREAN SECTION

6.4.1 Spinal anaesthesia

Today the majority of CS are performed in spinal opioid anaesthesia, which is regarded "golden standard" in absence of a working labour epidural to top up, described in ECS in study V (39-41). There are good evidence and recommendations, to use a mixture of local anaesthesia – commonly used hyperbaric bupivacaine 0.5%, with both lipophilic, fast action opioid, and hydrophilic, slow action opioid, to gain peri- and postoperative advantages (39, 40, 92-94, 106). Quality of CS spinal block is improved and volume of local anaesthesia can be reduced with supplementation of fentanyl 10-25 μg or sufentanil 2.5 or 5 μg resulting in less side effects from local anaesthetics, reduced need of perioperative analgesic supplementation, less nausea and more prolongation of analgesia in sufentanil 5 μg group, but to the expense of more pruritus mainly seen in sufentanil groups (92, 94). There are findings implying risk of acute opioid tolerance, caused by fentanyl diminishing the effect of ITM, since higher postoperative pain scores have been found when fentanyl is added to bupivacaine/morphine mixture (107). This is however not clarified, and the reduction of patients having intraoperative pain and requirement for intraoperative rescue medication must not be overlooked (94).

In UK diamorphine is used as adjunct to bupivacaine, having physiochemical properties resulting in fast onset of analgesia, as well as prolonged duration of analgesia due to high lipophilicity (octanol-water coefficient 280) and the active metabolite; morphine, providing the extended duration of analgesia (40). Diamorphine is not available in Sweden, but we found in study III majority of obstetric anaesthesia departments use a mixture of bupivacaine, fentanyl 10-20 μg or sufentanil 2.5-10 μg and morphine 100-125 μg as is recommended as "golden standard" for spinal CS anaesthesia. All 32 answering units used at least one intrathecal opioid but 14 of these units used sole one, lipo- or hydrophilic opioid as adjunct to bupivacaine; 2 units use sole ITM, 5 units use fentanyl and 7 units use only sufentanil (Table 10). When assessing the impact of different routines with respect to total performed CS in the obstetric anaesthesia units we found one-intrathecal-opioid-units representing 26% of

performed CS in Sweden, 55% supplementing bupivacaine with ITM and fentanyl and 2 % with ITM and sufentanil (Table 10, Figure 11). The rest 17% did not reply the questionnaire.

A few units in our study replied use of ITM only in elective situations. The rational for this is unclear and the literature support use of both a lipophilic opioid and ITM in emergent CS, even the most emergent situations as we studied in study V (40, 41). SA median time for DDI was 20 minutes with range between 13 minutes and 33 min. Three SA-CS exceeded the 30 minutes rule but with additional 1-3 minutes and the neonatal outcome was for all three cases 10 for Apgar at 5 min. and pH*a* 7.21-7.29.

There is higher risk of intraoperative pain and need of rescue medication during ECS both with spinal and epidural anaesthesia compared with elective CS (108). Addition of a lipophilic opioid will contribute to a shorter onset, thus time from decision to incision, and less risk of pain problems during the delivery, and thereby may reduce need of conversion to general anaesthesia (40, 108). There are arguments of time loss and risk of dosing-errors when mixture of several drugs is performed, which is to be considered. However the evidences of risk-benefits are in favour of adding a lipophilic opioid, producing an earlier onset and more profound anaesthesia, in the most emergent cases in accordance with our results in study V (24, 40, 41). Ngan et al. proposed a synergistic effect with intrathecal opioid-supplementation to local anaesthetics after study in labour (109).

A dose of 100 µg ITM is recommended in addition, as the hydrophilic opioid, prolongs the duration of post-operative analgesia, not provided by fentanyl and sufentanil (39, 40, 93, 106). ITM is very efficient decreasing pain and requirement of supplemental anaesthesia after abdominal surgery, and shown superior to oral and intravenous morphine and local anaesthetic techniques like TAP and wound infiltration (39, 100, 110). Severe post-operative pain after CS will contribute to, in addition to the discomfort, difficulties in mobilizing, causing thromboembolic risks and risks of ileus but is also a recognised risk factor for persistent pain (1, 2, 18).

6.4.2 Epidural anaesthesia

Epidural anaesthesia for CS is today usually chosen when there is a labour epidural in place to top up or in special cases in a CSE, when prolonged surgery is expected. Top up of labour epidural has been proven as fast as general and spinal anaesthesia (40, 41). We found in study V, GA faster than both SA and tEDA (10-13 minutes respectively) but with no statistical differences comparing SA and tEDA. We use a mixture of ropivacaine 0.75% 15-20 ml with supplementation of fentanyl 50-100 µg. Parate et al. found supplementation to bupivacaine 0.5% with 50 µg fentanyl providing significantly intraoperative reduction of pain, and rescue analgesic requirements with prolonged analgesia, and it is recommended to add a dose lipophilic opioid to local anaesthesia in a top up mixture (40, 111). In opposite to this Malhotra et al. found no benefits with addition of fentanyl 75 µg to epidural levobupivacaine, when extending labour epidural for elective CS (112). All the labour epidurals were

maintained with midwife administered boluses; 10-15 ml of bupivacaine 0.1% plus fentanyl 2 µg/ml as required up to half-hourly (112).

For epidural top up, different local analgesic mixtures have shown significant differences regarding onset of anaesthesia; Allam et al. halved the onset time with fresh mixture of lidocaine-bicarbonate-adrenaline compared with levobupivacaine to 7 (5-8) min. and 11 (9-14) min. respectively, with side effect of increased maternal sedation (113). Sodium bicarbonate is thought to facilitate passage across the neuronal membrane of lignocaine, with its low pKa. No additional lipophilic opioid was used to extend to surgical anaesthesia, and labour analgesia was maintained with bupivacaine 0.1% and fentanyl 2 µg/ml as 3 ml/h background infusion plus 5 ml boluses; 15 min. lockout-time in PCA (113). They conclude there are so many differences in studies; speed and volume of top up injection, definition and measuring of onset time, basic regimes during labour, and the study population, making it almost impossible to extrapolate results between studies (113). Lignocaine-adrenaline mixture without sodium bicarbonate has not shown this advantage in faster onset compared with bupivacaine. For a period lignocaine 2% for epidural use was not available in Sweden and we then changed to ropivacaine 0.75%, used in study V. Ropivacaine 0.75%, levobupivacaine 0.5%, and lignocaine-adrenaline-fentanyl mixture was compared by Sng et al. as top up of labour epidural, during labour maintained with ropivacaine 0.1% and fentanyl 2 µg/ml 10 ml/h, for urgent CS, and no significant difference was found regarding onset time (114). They found median onset time was 10, 10 and 9.5 min respectively, defined "start of anaesthesia to ready for surgery", which is in line with our onset time in study V (114).

Seven tEDA-CS exceeded the 30 minutes rule with additional 1-11 minutes with the neonatal outcome for Apgar at 5 min. 9 for one, and 10 for the other six, and median pH*a* 7.22 within range 7.13-7.29.

After delivery we routinely add morphine 2 mg in tEDA to prolong postoperative analgesia. However we studied only the initial timeframes of the ECS and did not follow the patients protracted, with a broader outcome and this is a limitation. Addition of epidural morphine was studied and compared with parenteral opioids in elective CS by Bonnet et al. In that systematic review they conclude epidural morphine increase quality of analgesia after elective CS during the first postoperative day, but with increased side effects, like pruritus and nausea and recommend a 4 mg dose of epidural morphine for good pain relief (115). In a multimodal concept Singh et al. compared two different doses of epidural morphine, 3 mg and 1.5 mg and found similar effect regarding pain and rescue opioid consumption, of halving the dose, but reduced side effects (116). Vora et al. studied both onset of analgesia and duration after CS, performed in epidural analgesia, by comparing three groups with postoperative addition of sufentanil 50 µg, morphine 4 mg or mixture sufentanil 25 µg plus morphine 2 mg (117). They found the combination of sufentanil and morphine producing a more rapid onset and a longer duration of analgesia, with less side effects, than the either of the two drugs alone (117).

We found in study III, 12/32 obstetric anaesthesia units supplement with morphine, corresponding to 37 % with regard to impact of performed share of CS in Sweden, 10 of these units using a 2 mg dose. Sufentanil was the most common lipophilic opioid used in epidural anaesthesia for CS, used in 15 units (39%) to compare with fentanyl, used in 10 units (25%). Most common dose of sufentanil was 5-10 µg and fentanyl 50-100 µg.

It is reasonable to believe there are mothers in Sweden that would benefit from receiving a dose of epidural morphine 1.5-2 mg to increase quality of analgesia after CS in units not using it.

6.4.3 Emergent CS

We found a DDI < 30 minutes was achieved in absolute majority of ECS, 92%, and our anaesthetic service in line with guidelines 24/7 in study V. This is superior compared to findings in 2014 by Tolcher et al.; 79% of category 1 CS and 36% of category 2 CS were performed within 30 min. The ten RA CS that exceeded 30 min. in our study, had all good neonatal outcomes. GA had the shortest DDI; 10 min., spinal 20 and tEDA 23 min. with no significant difference seen between SA and tEDA.

Unfortunately we collected information only about the conducted anaesthesia in study V, and we are not able to conclude the amount of intended, supplemented with analgesics and/or failed regional anaesthesia, if any. Change of anaesthesia was not included in protocol though it is an important view to control and this is a limitation. If registered, the reason for changing anaesthesia may be difficult to truly sort out in the emergent situation, since the maternal or foetal situation may deteriorate quickly, or be hard to diagnose, the obstetrician may feel distressed by waiting even for few minutes for anaesthesia to be established, though full analgesia is expected in short time (41, 118). The role of good communication is central, to be prepared and pre-informed, about patients at risk for ECS is best in view of anaesthetists, patients and the whole team. Trust and co-operation within the team are most important, never overvalued (40, 41, 118).

The obstetrician decides within what time delivery is needed, and anaesthetist what anaesthesia is best to use according to this with regard to the mother. General anaesthesia is chosen for the most urgent CS and, not surprisingly, associated with shortest DDI in our findings, but in general also conducted with increased risk for the mother; risk of failed intubation, aspiration, other respiratory complications, but the risk difference between GA and RA has decreased during the years (50, 119, 120). GA during CS is also associated with higher risk of persistent pain (2). Epidural and spinal anaesthesia offer the opportunity to add low dose of morphine to provide effective postoperative analgesia with long duration superior to oral, invasive or local analgesic peripheral methods, but with some increase in side effects (17, 24, 39, 115).

We strive to use GA for ECS only when regional anaesthesia is contraindicated or at those indications that really need immediate delivery, which is a much more complicated process than it may first appear to the anaesthetist and rest of the team involved (40, 41, 118). For

emergent CS where delivery is estimated not immediate but with need within 30 minutes, we have worked with the whole process to minimize time-shares and for all included moments between decision and delivery; information to anaesthetist, call and gathering of the surgical team, transport of patient to OR, start of anaesthesia, time to anaesthesia is established, incision (=start of operation) and delivery. To use this time optimally for most important actions, get the best quality from this time, is crucial. As described in study V this includes as far as it is possible, to have information about patients at risk in advance, and if possible to establish a labour epidural as well, and be informed if any problems show up. The obstetrician calls and informs the anaesthetist (specialist) directly after decision of ECS, including existing labour epidural, and then press the alarm to gather the team to the OR especially reserved for ECS. When the team is gathered the obstetrician have a second opportunity to decide whether there is need to deliver immediately or within 20-30 minutes, often after CTG is controlled. In Table 15 CS indications are listed along with used anaesthesia. However the CS indication alone does not give us enough information about how urgent the delivery is within the theoretical 30-minute rule. The obstetrician has to, in a short time deal with a more complex decision including information about history of CTG, lactate tests, the foetal growth and maturity and the mother etc.

Our data, DDI time and neonatal outcome imply the process of decisions, obstetrical and anaesthesia including mutual communication and logistics, is well working. Apgar-score at 5 min. <7 was more frequently seen among neonates in GA group; 11/64 to compare with 2/30 in SA group, and 1/41 in tEDAgroup ($p<0.05$). We also found neonatal pH <7.1 more frequently among deliveries having GA than RA; 14/64 compared to 2/30 with SA and 1/41 having t EDA, all 3 RA with DDI within 30 min. This is an observational study without intervention and we interpret the neonatal data associated with anaesthetic technique as the fastest anaesthesia; GA is adequately chosen for the most urgent cases with highest foetal distress. This is in line with findings of Blom et al. showing CS performed within 30 minutes were associated with more compromised new-borns, and Dunn et al. comparing GA and RA, found GA associated with shorter DDI and a worse perinatal outcome (121, 122).

If indicated the mother receives terbutaline before or after decision, as intrauterine foetal resuscitation, but we did not within study V collect information about tocolytics administration, which is a limitation. Neither did we analyse number of patients experiencing hypotension nor amount of consumed vasopressor. When the anaesthetist gets information about labour epidural in place, topping up is usually started in the delivery room or when patient is on its way to OR within short reach, by the anaesthetist, who stay monitoring the patient. During the topping up, foetal heart rate monitoring is continued and with improved FHR pattern the need of urgency decreases. These are factors that might affect DDI time.

6.5 INTRATHECAL MORPHINE AND SIDE EFFECTS

When 100 women are administered 100 μg ITM Dahl et al. assessed number of patients experiencing pruritus, vomiting and nausea to be 43, 12 and 10 respectively (93). Bonnet et al. found increased incidences of pruritus and nausea after epidural morphine (115). They still

recommend use of a 100 µg ITM and a 4 mg dose of epidural morphine respectively to provide good pain relief after CS (93, 115).

In Study III only 20/32 units, corresponding to 61% when assessing the impact of routine with regards to the performed CS in those units, were using ITM in Sweden. We find the difference in routines in study III surprising, implying there are possibilities to improve peri- and postoperative treatment with regard to Carvalho et al. findings about patients preferences for anaesthesia outcomes in caesarean delivery where intra- and postoperative pain is most feared (86).

We did not observe difference regarding side effects between groups in study I or II, with exception for pruritus, seen only in groups receiving ITM. No patient in any of our studies experienced severe adverse event, no respiratory depression needing naloxone, but the studies were not powered to detect side effects. Meylan et al. performed a meta-analysis regarding ITM benefits and risks and found increased incidence of pruritus [OR 3.85 (95% CI 2.40–6.15)] and of respiratory depression [odds ratio (OR) 7.86 (95% CI 1.54–40.3)] but with no clear linear dose-responsiveness (110).

6.5.1 Respiratory depression

From the obstetric anaesthesia units in Sweden withholding morphine in study III, the reason was fear of late respiratory depression or problems to monitor, answered by 7/12 units. Risk of respiratory depression with morphine, neuroaxial and systemic use, must be acknowledged but the risk with use of neuraxial morphine anaesthesia with doses limited to < 200 µg may have become excessively emphasised due to doses used in the 80ths. With a dose < 300 µg, respiratory depression is proposed not more frequently occurring than with systemic use of morphine, but with ITM, rare but more challenging late respiratory depression occurs (24, 123). Most of the large obstetric units in Sweden have, as in our hospital, implemented routines for prolonged monitoring as recommended by SFAI, with the first 2-6 hours either in postoperative care or delivery ward, and following hours, up to at least 12 hours, in regular maternity ward. Unfortunately we did not ask further questions about routines of pain treatment and outcome, but multimodal neuroaxial opioid anaesthesia, including paracetamol and NSAID is proven superior to pain treatment models based on oral and intravenous morphine, TAP and wound infusion catheters (39, 100).

In Danderyd hospital we have had the routine for 17 years to administer 100 µg ITM to hyperbaric bupivacaine 11-12 mg and 10 µg fentanyl for CS spinal anaesthesia in a multi modal concept along with paracetamol and NSAID at a regular base, producing generally good pain-relief and few complaints of side effects. To our knowledge there is no known severe side effect occurrence, no known case of respiratory depression needing naloxone, during these years. Anecdotally midwives reacted surprised and satisfied when the routine was introduced and wondered about “the remarkable effect” that made earlier mobilization possible and by their judgement, higher maternal satisfaction. Still among obese mothers there is a greater risk of post-operative respiratory impairment, which can be aggravated by

ITM. We wanted in depth to explore obese mothers the night after morphine spinal CS, and whether polygraphy equipment used in OSA-diagnosing would be of help in revealing pathologic breathing pattern, not detected by our routine monitoring (10, 43).

We consider our findings in study IV as normal/mild in this at risk cohort; moderately obese mothers postoperatively the night after caesarean section in spinal anaesthesia with 100 µg ITM and 10 µg fentanyl. All but 2 mothers showed an AHI well within normal (n=11) and mild (n=7) ranges and 2 had values in the lower edge of moderate zone (15.3 and 18.2). No mother was found having AHI defined as severe sleep apnoea. Even mild or moderate sleep apnea may cause adverse effects, and preoperative screening and testing for sleep apnea in accordance with guidelines is recommended, to find women who would gain from treatment with continuous positive airway pressure (124). However we found postoperative respiratory polygraphy cumbersome and it seems not to provide much critical information. Upper airway compromise with obstructive hypo- or apnoea was not frequently seen in this group of moderately obese mothers. Mothers with a high AHI did not show typical high oxygen desaturation index or $TcCO_2$ elevation. The two devices used showed somewhat different AHI ODI correlation. The Nox device showed a correlation between AHI and ODI 0.7 with the ODI providing higher indices, the Embletta showed a correlation 0.78 with AHI showing higher indices. We are not able to further in depth assess these differences. It may be regarded as a limitation that we used different polygraphic equipment, during the study. The Embletta was used routinely in sleep apnoea screening in our department at the time of start of study IV but was changed to Nox after first eight patients were examined. We found the Nox smaller and easier for the mothers to cope with, and we assessed it provided information as good as that of the Embletta.

Short episodes of oxygen desaturation were observed, but whether these events were related to bradypnea, or shallow breathing, we are unfortunately not able to assess. None of the mothers showed a transcutaneous carbon dioxide elevation, no registration above 5.9 kPa, thus all mothers had normal values of $TcCO_2$. The $TcCO_2$ monitoring was however not set for detecting brief episodes of CO_2 elevation, since it had a 5-minutes averaging algorithm. Respiratory depression is known to progress slowly (24). Also the screening ESS scores were low, 3 mothers scored more than 10, commonly assessed as threshold value.

There are few studies with polygraphy registration sleep apnoea, associated with ITM. The effects of 30 mg oral morphine and effects of remifentanil infusion were assessed in different studies, on patients with mild to moderate obstructive sleep apnoea and showed paradoxically that opioids may improve sleep apnoea, but oxygenation was worsened by remifentanil infusion (125, 126). Respiratory effects of 300 µg dose of ITM to patients having orthopaedic operations under spinal anaesthesia were studied in a RCT concept and Cole et al. found in similarity to us that night time polygraphy is cumbersome, similar incidence of apnoea /hypopnea episodes in both groups, but lower mean oxygen saturation in the ITM-group (127). Likewise in a Cochrane review, assessing the effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea, none of

the studied drugs produced a significant increase in AHI or ODI and two trials even showed a beneficial effect (128). However catastrophic events are described related to obesity, undiagnosed sleep apnoea, opioids, sedatives and lack of monitoring (129).

We found polygraphy as postoperative monitoring after CS of limited value. Monitoring of respiratory rate, transcutaneous oxygen and carbon dioxide measure may be more feasible (130-132). Oximetry after CS with 150 µg ITM showed frequent mild desaturation events and increased risk in patients with obesity (130). Transcutaneous CO_2 postoperative monitoring after CS with similar dose, 150 µg ITM showed frequent hypercapnia events, defined >50 mm Hg for ≥2minutes duration, and higher baseline$TcCO_2$ readings (131). Dalchow et al. found Tosca® $TcCO_2$ monitoring after CS detecting respiratory depression (>7 kPa for >2 min) in a higher incidence compared to desaturation (<90% for >2 min) (132).

There are several limitations with study IV. We have few registrations, only 20 mothers with satisfactory registration. We had difficulties including obese parturients. In our hospital we perform about 1100 elective caesarean sections every year. The amount of obese parturients in this group is not known but with 8.7% obesity in pregnancy in Stockholm we assume a number of 90-100 would be likely every year. Among these obese mothers language difficulties are not uncommon; not possible to include. In addition some declined participation, understandable in this unique situation, becoming parent. The low incidence of obesity also explains the, in terms of obesity relative low BMI (mean 35) in our study and a higher BMI and more patients would have been of interest. With the portable polygraphy we are not able to assess sleep time or if the mothers were merely resting, that requires full polysomnography, but the polygraphy equipment has shown similar diagnostic information but may underestimate sleep apnoea severity (133).

Preoperative assessment for sleep apnea should be performed in at risk patients, eventually including polysomnography (134). How to screen for OSA during pregnancy is however not well defined. Berlin questionnaire or Epworth sleepiness scale was found poorly predictive of OSA among pregnant women and associated with high false referral rate (135). For pregnant obese women, especially in case of hypertension and preeclampsia, snoring and/or gestation diabetes, that are associated with increased incidence of OSA, assessment seems warranted earlier during pregnancy since untreated OSA may affect maternal and foetal outcome (134, 136, 137). Detecting these women at risk and offering them treatment with continuous positive airway pressure, has shown promising results, like decreased hypertension and less preeclampsia development (138, 139). This handling would also decrease risk of meeting undiagnosed OSA obstetric patients at risk postoperatively.

7 CONCLUSIONS

- Intrathecal morphine in doses of 100 µg or less, as supplement to bupivacaine and sufentanil spinal analgesia for labour pain, was not found advantageous regarding duration, onset of analgesia or impact on following epidural doses.
- Intrathecal morphine as supplement to bupivacaine, for postoperative pain after abdominal hysterectomy, reduces first 24 hours post-operative PCAmorphine consumption and pain (VAS). We found additional effect of 200 µg compared to 100 µg but no advantage from increasing the dose to 300 µg.
- Intrathecal/epidural morphine, fentanyl and sufentanil use is widely spread in Sweden as supplement in spinal anaesthesia for mainly CS and abdominal hysterectomy but varying regimes exist. A majority combine lipophilic opioid (fentanyl or sufentanil) with rapid onset with hydrophilic, long-acting morphine, but some anaesthesia units use solely lipophilic opioid and some use only hydrophilic morphine as adjunct to local anaesthesia.
- Risk for respiratory depression and difficulties in monitoring are still considered main reasons for restricting use of intrathecal/epidural morphine in some units in Sweden.
- Postoperatively during the night after caesarean section in spinal anaesthesia including low dose intrathecal morphine, short episodes of mild oxygen saturation decrease were observed in moderately obese mothers, but upper airway collapse, obstructive hypo- or apnoea – high AHI - was not found.
- We found sparse clinical benefit in using portable polygraphy as postoperative respiratory monitoring in obese mothers first night after caesarean section in spinal anaesthesia with low dose intrathecal morphine.
- We found spinal anaesthesia with bupivacaine, morphine and fentanyl mixture, as well as top-up labour epidural provided similar rapid time to delivery and seem a reasonable benefit vs. risk option for category 1 and 2 ECS with acceptable DDI within 20–30 minutes.
- We found no reason to exclude intrathecal morphine in the emergency caesarean service.
- General anaesthesia was, as expected, associated with a more rapid DDI, 10-13 minutes faster vs. spinal and top up epidural respectively, with no difference observed between RA-methods.

8 FUTURE PERSPECTIVE

- RCT: Intrathecal addition of morphine 100 µg to patients' postpartum revision operations after maternal vaginal traumatic births. Observe differences regarding occurrence of acute and persistent pain.

- RCT: Before removing the epidural catheter add 2 mg of morphine to mothers having had vaginal birth. Observe differences regarding occurrence of acute and persistent pain.

- RCT: Laparoscopic robotic gynaecologic surgery including hysterectomy – addition of 0, 100, or 200 µg of ITM. Observe differences regarding occurrence of acute and persistent pain, postoperative morphine consumption, mobilization and hospital stay and persistent pain.

- Observation of pain after CS, a prospective study, elective and emergent CS, with respect to acute and persistent pain, indication, different anaesthesia, postoperative analgesia, pain before CS, surgical approach, time of day and neonatal outcome.

- Observation study/ RCT, including women during pregnancy, with BMI > 30, with hypertension, snoring and/or gestational diabetes. Screening use of polygraphy registration during sleep and CPAP treatment if positive findings. Follow through pregnancy – outcome – maternal, foetal and CS rate? Postoperative complications?

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund: Smärta är ett kliniskt problem i samband med förlossning och postoperativt efter kejsarsnitt och operationer där livmodern opereras bort. Det finns flera anledningar, både humana och ekonomiska till att minimera smärtan då smärtan med minskat välbefinnande, påverkar hela förlossningsupplevelsen och det postoperativa förloppet, och förlänger vårdtiden på sjukhus. Otillräcklig smärtbehandling är en riskfaktor för långvariga smärttillstånd (1, 3). Multimodal smärtbehandling, där man kombinerar olika läkemedel med olika mekanismer för att nå adderad eller synergi effekt som minimerar både smärta och också biverkningar är idag rekommenderad praxis (16). Användandet av låg dos morfin i ryggbedövning kan ge god smärtlindring med långvarig effekt, men användningen begränsas av biverkningar där risk för försämrad andning är den mest fruktade (34, 38, 76). Fetma, övervikt medför ökad risk för påverkan på andningen, nedsatt andning och ökad risk för s.k. sömnapné. Fetma ökar också risken för andningsdepression av morfinpreparat, vilket sammantaget innebär ökad risk för försämrad andning efter kejsarsnitt där man använt spinal bedövning med tillsats av morfin (10).
Syftet med dessa studier var att undersöka effekterna av en liten dos morfin som tillägg i ryggbedövning ur olika aspekter; vid smärtlindring med spinal bedövning under förlossning, i spinalbedövning vid livmoderoperation för förbättrad smärtlindring efteråt, kartlägga användandet av morfin i ryggbedövning i Sverige, utreda om utrustning som används för utredning av sömnapné kan förbättra kunskapen om andningspåverkan hos överviktiga mödrar efter kejsarsnitt i ryggbedövning med morfin och slutligen användandet av olika anestesimetoder, generell och regional anestesi med morfin vid omedelbara och brådskande kejsarsnitt.

Metoder and Resultat: Studie I and **II** är randomiserade (= lottade till olika grupper för olika behandling) dubbel-blindade (=vare sig undersökare eller patient vet vid undersökningen vilken behandling patienten får) placebokontrollerade (= En av behandlingsgrupperna får placebo) undersökningar av effekterna av att ge olika doser av morfin som tillägg till lokalbedövning i spinalbedövning.

I **Studie I** jämförde vi tillägg av morfin 50 eller 100 µg eller placebo till bupivakain (1.25 mg) och sufentanil (5 µg) för att värdera om morfin förlängde tiden som patienterna var smärtlindrade av ryggbedövningen. Nittio först-födande kvinnor i förlossningsarbete fick en kombinerad spinal- epidural bedövning och vi bedömde tiden som patienterna var smärtlindrade av spinalbedövningen, som tiden från injektionen till smärta återkom i styrka enligt VAS > 4. Vi fann inga skillnader mellan grupperna avseende tid till smärtlindring, tid till dess smärta återkom, biverkningar, förlossningsförlopp eller utfall för barnet.

I **Studie II** lottades 144 friska kvinnor, som skulle genomgå bortoperation av livmodern i kombinerad ryggbedövning och narkos, till fyra grupper där samtliga i spinal fick lokalbedövning – bupivakain tung 12 mg kombinerat med 100, 200 och 300 µg morfin eller koksalt. Vi undersökte effekten av smärtlindring dygnet efter operationen, genom att kontrollera mängden morfin patienten behövde både givet av sköterska och från patientstyrd

pump. Morfintillägg i spinalbedövning minskade morfinkonsumtionen postoperativt, 100 µg minskade morfinbehovet efter operationen signifikant jämfört med placebo vid 0-6, 6-12 och under hela mätperioden 0-24 timmar. Morfindosen 200 µg minskade signifikant ytterligare det intravenösa morfinbehovet jämfört med 100 µg vid 0-6 timmar och för hela mätperioden 0-24 timmar. Däremot sågs ingen ytterligare skillnad med morfin 300 µg jämfört med 200 µg. Illamående var lika vanligt i alla grupper. Klåda sågs endast i morfingrupperna. Inga allvarliga bieffekter förekom: ingen patient fick försämrad andning.

I **Studie III** kartlades hur stor användningen är av morfin och övriga opioider är givet i spinal och epidural, till huvudsakligen kejsarsnitt och vid bortoperation av livmodern på sjukhus i Sverige. Vi sände en enkät till narkosläkare ansvariga för obstetrisk anestesi vid samtliga förlossningssjukhus i Sverige och erhöll svar från 32 av 47 enheterna (68%). Vid kejsarsnitt använde 20/32 enheter morfintillägg i spinal med vanligaste dos 100 µg (17/21). Vid kejsarsnitt i epidural använde 12/32 kliniker morfintillägg med vanligaste dos 2 mg. Vid bortoperation av livmodern använde 20/32 enheter morfin i spinalbedövning och 9/32 använde 200 µg. Risk för andningsdepression/ svårigheter att övervaka angavs som anledning att avstå morfin i ryggbedövning.

Studie IV är en beskrivande observationsstudie för att undersöka förekomst av sömnapné bland överviktiga mödrar postoperativt första natten efter kejsarsnitt i spinalbedövning med morfintillägg, och om portabel utrustning för sömnapné kan tillföra kunskap och användas i övervakning i denna grupp. Bland de 20 mammor som genomförde andningsregistreringen hade 11 (andningsuppehålls index) AHI <5 (normalt); 7, AHI ≥5 - <15 (lätt ökat); och 2, AHI ≥5 15 (moderat, 15.3 and 18.2). Vi fann inte något samband mellan AHI och ODI (syremättnads index) eller tecken på förhöjda koldioxid värden mätt genom huden. Medel värdet för ODI var 4.4 (normalt) men åtta mammor hade värden >5. Medel syremättnad var 94 % (91-96%) och fyra mammor hade medelvärden mellan 91-94% men ingen hade < 90%. Ingen av mammorna visade tecken på allvarligt sänkt andningsfunktion i kliniska rutinkontroller. Allvarlig påverkan på de övre luftvägarna var inte vanligt förekommande första natten efter kejsarsnitt hos mammor med ett BMI >30 som fått 100 µg morfin i spinalbedövning tillsammans med 10 µg fentanyl för kejsarsnitt.

Studie V är en retrospektiv genomgång av akuta larm kejsarsnitt vid Danderyds sjukhus under januari – oktober 2016 med syfte att bedöma tiden från beslut om kejsarsnitt till barnet är förlöst (DDI) och påverkan av vald anestesi, generell (GA), spinal (SA) med tillägg av opoid eller ”top up” av förlossningsepidural (tEDA) med lokalbedövning och fentanyl blandning) och arbetsskift. Totalt analyserades 135 kejsarsnitt, 92 % förlöstes inom 30 minuter och medel DDI var 17.3±8.1 minuter. GA förkortade DDI med 10 minuter och 13 minuter jämfört med spinal respektive tEDA ($p<0.0005$). Det var ingen skillnad i DDI för spinal och epidural och inte heller beroende på tid på dygnet eller veckodag. Apgar <7 vid 5 minuter var vanligast vid kejsarsnitt i GA (11 av 64) jämfört med spinal (2/30 och tEDA (1/41) ($p<0.05$).

Slutsats: Lågdos morfin i spinal ryggbedövning har en betydelsefull roll för att optimera postoperativ smärtlindring i ett koncept för tidig återhämtning efter operation, vid planerade och akuta kejsarsnitt och vid bortoperation av livmodern. Morfindoser i spinal ryggbedövning över 200 µg förefaller inte ge mer smärtstillande effekt men kan öka risken för biverkningar. Om spinalbedövning används som förlossningsbedövning är tillägg av morfin i dos 100 µg eller mindre inte meningsfull för att förlänga durationen. Användning av morfin i spinal är spridd i Sverige och vanlig framför allt till kejsarsnitt och bortoperation av livmodern men är fortfarande begränsad inom vissa enheter, av oro för försvårad andning eller svårigheter att övervaka postoperativt. Monitorering av överviktiga mammor (BMI>30) visade inte någon mamma med allvarlig sömnapné (OSA) utan generellt normal eller mild påverkan och endast två mammor hade apné/hypopné värden (AHI) strax över gränsen till moderat OSA i vårt begränsade material. Utrustning för nattregistrering av sömnapné synes vara av begränsat värde postoperativt, och inte tillföra något utöver den information som fås av andningsfrekvens och transkutan koldioxidmonitorering natten efter kejsarsnitt i spinal med tillägg av morfin, men kan behövas göras i ökad omfattning preoperativt eller tidigare under graviditeten. De mest akuta kejsarsnitten kunde förlösas inom 30 minuter i 92% och generell anestesi förkortade tiden från beslut till förlossning med 10 och 13 minuter för spinal respektive top up epidural bedövning. Ingen tidsskillnad sågs mellan spinal eller epidural bedövning eller påverkan av tid på dygnet.

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