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# Opioid reducing strategies in post-operative pain management

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*To my family*

# Abstract

Adequate pain treatment is motivated by humanitarian grounds. It also seeks to reduce morbidity, improve recovery and diminish risks of persistent postoperative pain. The present Study I evaluates patient-controlled analgesia (PCA) against conventional nurse-administered opioid therapy. Studies II to IV are randomised, placebo-controlled investigations of pain severity and opioid consumption following breast-cancer surgery and caesarean section in women treated with a combination analgesic approach.

**The general aim** was to investigate strategies for reduced pain and opioid consumption in patients suffering moderate-to-severe postoperative pain.

**PCA evaluation and early versus long term pain:** Self-administration of opioids after breast cancer surgery was compared to conventional nurse-administered opioid treatment in 144 women. Effect variables were pain intesity and opioid requirements. Four years after surgery, patients completed a questionnaire regarding persistent pain. Patient-controlled analgesia provided better pain relief with higher opioid consumption postoperatively. The prevalence of pain persisting after 3-4 years was 25%. In conclusion: PCA technique was superior to conventional nurse-controlled intravenous treatment in relieving pain after breast cancer surgery at higher opioid consumption. Immediate breast reconstruction (IBR) generates intense post-operative pain that responds poorly to opioids. Axillary dissection however is more predictive of persistent pain.

**Diclofenac after caesarean delivery:** Pain after caesarean section is related to uterine contractions poorly responsive to systemically administered opioids. As non-steroidal anti-inflammatory drugs (NSAIDs) have good effect on menstrual pain thought to affect uterine pain mechanisms, we studied how far the required dose of opioids could be decreased by adding diclofenac – an NSAID – to opioid PCA, in 50 women delivered by caesarean section. Ketobemidone demand was 39% less in the diclofenac group. No patient had bleeding complications after surgery. In conclusion: 150 mg diclofenac as an adjunct reduced the need for opioids significantly during the first 24 h after caesarean delivery, with maintained or improved analgesic effect.

**Diclofenac after mastectomy and IBR:** Aiming at satisfactory rest and functional pain relief for 64 hours after IBR we studied diclofenac as an adjunct to paracetamol and opioid PCA in 48 women. Primary outcome measures were pain intensity at rest and on movement and opioid consumption. Secondary outcome measures were per- and postoperative bleeding, nausea and tiredness. Pain relief at rest was significantly less for 20 h with diclofenac. During movement there was a non-significant difference. Opioid consumption the first 6 h postoperatively was significantly – 34% – less in the diclofenac group. Postoperative bleeding was greater with diclofenac than with placebo. In conclusion: D iclofenac 150 mg/24 h added to paracetamol and opioids, reduced opioid consumption for 6 hours and improved pain relief during the first 20 h at rest but was not convincingly effective during mobilisation. Postoperative blood loss was higher with diclofenac.

**Local anaesthesia after delayed breast reconstruction (DBR):** Forty-three women earlier undergoing surgery for breast cancer and scheduled for unilateral DBR with subpectoral tissue expander implant were investigated. The purpose was to evaluate the analgesic efficacy of local anaesthesia (levobupivacaine) via an indwelling catheter in the operation area every 3 h for 45 h in combination with paracetamol and opioid PCA. Effect variables were pain intensity at rest and on mobilisation, and opioid consumption. The levobupivacaine group reported significantly lower pain intensity at rest during the first 15 hours after surgery. During mobilisation there were significant positive differences in pain in this group for the first 6 hours and for the time interval 18-24 hours post-surgery. Total opioid consumption was not significantly lower. In conclusion: Local anaesthesia in addition to opioids and paracetamol improved pain relief at rest and on movement after DBR, with a non-significant reduction in need for opioids.

**The general conclusion** is that the drug combinations investigated resulted in reduced opioid consumption and improved pain relief in patients suffering moderate-to-severe postoperative pain.

# List of Papers

I Legeby M, Segerdahl M, Sandelin K, Wickman M, Östman K, Olofsson C.
**Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain.**
*The Breast* 2002; 11: 156-62.

II Olofsson C, Legeby M, Nygårds E-B, Östman K.
**Diclofenac in the treatment of pain after caesarean delivery An opioid-saving strategy.**
*Eur J Obstet Gynecol Reprod Biol* 2000; 88: 143-6.

III Legeby M, Sandelin K, Wickman M, Olofsson C.
**Analgesic efficacy of diclofenac in combination with morphine and paracetamol after mastectomy and immediate breast reconstruction.**
*Acta Anaesthesiol Scand* 2005; 49: 1360-6.

IV Legeby M, Jurell G, Beausang- Linder M, Olofsson C.
**Analgesic efficacy of local anaesthesia in combination with morphine and paracetamol after breast reconstruction with submuscular implant.**
*Manuscript.*

# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| ALND | Axillary lymph node dissection |
| ANOVA | Analysis of variances |
| APS | Acute Pain Service |
| CNS | Central Nervous System |
| COX | Cyklo-oxygenase |
| DBR | Delayed breast reconstruction |
| IASP | International Association of Pain |
| IBR | Immediate breast reconstruction |
| LTP | Long term pain |
| M | Mastectomy |
| ML | Maestectomy and axillary lymph node dissection |
| MR | Mastectomy and reconstruction |
| MRL | Mastectomy, reconstruction and axillary dissection |
| NA | Nurse administered |
| NMDA | N-methyl-D-aspartate |
| NO | Nitric oxide |
| NRS | Numerical rating scale |
| NSAID | Non steroidal anti-inflammatory drug |
| PCA | Patient controlled analgesia |
| TRAM | Transverse rectus abdominis muscle |
| VAS | Visual analogue scale |
| VRS | Verbal rating scale |

# INTRODUCTION

Pain is a subjective, unpleasant experience that varies in character, intensity and meaning to the individual. Pain management in hospital is very complex, involving individual aspects and also organisational and ideological ones [47]. Historically, it has been debated how far pain is purely stimulus-provoked; a behavioural, emotional or multidimensional phenomenon. Definitions through the years can be classified according to which was considered predominant at the time.

The modern view of pain is based on its subjective nature and on the following definition by the International Association for the Study of Pain [112]: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Pain relief has been a medical interest for decades yet surveys still demonstrate a high prevalence of unacceptable pain in hospitalised patients [26 4 17 145 37 161 86]. Interest has not resulted in efficacious treatment, although there are intentions towards pain-free hospitals [109].

The purpose of the present work was to examine mainly postoperative pain treatment. The prevalence of persistent pain years after breast surgery was also investigated.

## Physiological aspects of postoperative pain

*The pain pathway*

Acute and postoperative pain is usually related to tissue damage and arises from activation of receptors, nociceptors with varying sensitivity to different kinds of stimuli. The nociceptors constitute the distal parts of myelinated A-delta nerve fibres and unmyelinated C-fibres. These first-order neurones have their cell bodies in the dorsal root ganglions and project distally into the tissue they innervate and centrally into the dorsal horn in the spinal cord. Nociceptors can be activated by mechanical, chemical or thermal stimuli. Some nociceptors are normally insensitive, "silent" but become mechanically and thermally sensitive and can be activated under chemically altered conditions [108]. First-order neurones synapse with second-

order neurones in the dorsal horn. The majority of the latter axons cross the spinal cord, ascend in the spinothalamic tract and synapse in the brain stem or thalamus with third-order neurones. These neurons project to different parts of the cerebral cortex as well as to sub cortical structures, resulting in pain being perceived (Figure1).

The complex pathway of an afferent message induced by an acute noxious stimulus is mediated by numerous substances and events at different levels in the peripheral and central nervous systems. Parallel to the sensory discriminative capacity of these systems, an affective-motivational component follows the three-neurone pathway. In addition a descending pain-modulating system has inhibitory effects on dorsal horn neurones. Moreover the entire system is plastic i.e. can modify its function according to different conditions [149] [151]. There is also evidence that persisting changes in the nervous system itself can be caused by peripheral and central activity [63].

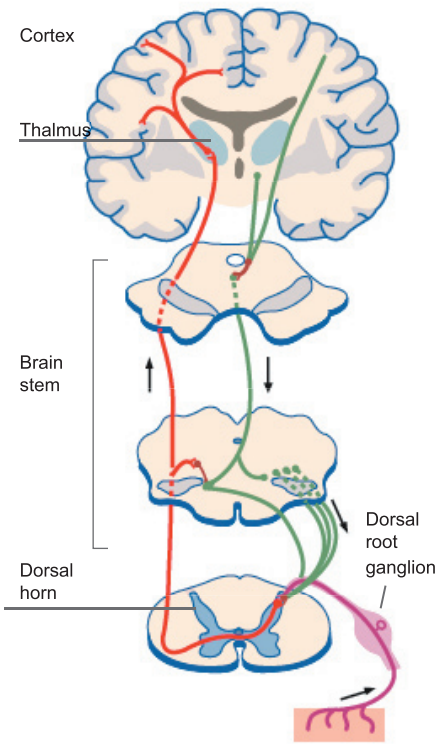


**Figure 1.** *Ascending pain pathway and descending pain-modulating system.*
*(Illustration Annika Röhl)*

*Plasticity and sensitisation*

Tissue injury peripherally induces the release of inflammatory mediators including ions; bradykinin, histamine, substance P, $K^+$, $H^+$ and others which excite A-delta and C nociceptors and/or increase their sensitivity at and near the site of inflammation. This *peripheral sensitisation* results in an increased response to noxious stimuli in the injured area (primary hyperalgesia). Prostaglandins released from injured and inflammatory cells are important mediators of inflammation, fever and pain. They contribute to pain by directly activating nociceptors in some situations, but are generally considered to be sensitising agents [117] [143]. With healing, this form of local hyperexcitability subsides.

Although inflammatory pain arises partly from peripheral processes, central sensitising mechanisms are also

involved. Nociceptive stimuli in the periphery induce changes in the sensory processing in the spinal cord. Surgery, muscle ischaemia or nerve cutting profoundly enhance neuronal activity in the dorsal horn, the brain stem and the brain [150] [76]. This activity-dependent *central sensitisation* is characterised by reduction in pain threshold and enlargement of the neurones' receptive fields (secondary hyperalgesia) [29] [183] [184]. The process in the dorsal horn synapses involves activation of the N-methyl-D-aspartate (NMDA) and tachykinin receptors via glutamate, substance P and neurokinin -1 [39] [120]. NMDA activation leads to calcium influx into the post-synaptic second-order neurones. This starts a chain of events which results in the production of nitrous oxide (NO). NO is necessary for normal nerve function but excessive production can lead to neurotoxicity [150]. Central sensitisation induced by noxious stimuli refers to a facilitation of this synaptic transmission in the dorsal horn neurones, leading to a reduction in pain threshold [65].

Additionally, when A-beta mechano-receptors (touch fibres) are activated pain can be perceived as a result of changes in sensory processing in the spinal cord. These changes result in pain produced by a low-threshold stimulus such as light touch (allodynia). Central sensitisation can outlast the stimuli by hours and if the stimulus is maintained the central sensitisation persists [50] [80].

Another NMDA-related form of plasticity is the 'wind-up' phenomenon described by Mendell 1965. Stimuli strong enough to activate C-fibres activate the dorsal horn neurones, but also change neuronal response properties. This results in progressively increased activity following repeated stimulation as long as the stimulus lasts [110]. This causes increasing pain intensity even though the stimulus intensity does not change [131] [158].

Understanding central changes induced by peripheral injury or noxious stimulation is of great interest in post-operative pain treatment for identifying type of pain or pain components – a prerequisite for adequate pain management [8] and prevention of long-lasting pain [25] [149] [76].

## Instruments for measuring pain

*Visual analogue scales –VAS*

The visual analogue scale (VAS) commonly used in pain studies and in the clinic consists of a 100-mm horizontal line with anchors labelled "no pain" and "worst pain imaginable" or similar descriptors [61]. The patient is required to mark a point on the line corresponding to the currently experienced pain. Visual analogue scales are presumed to measure the sensory intensity dimension of pain. The VAS is reliable and valid for experimental and clinical use, chronic and acute pain. It is sensitive to small fluctuations in pain

intensity due to pharmacological and non-pharmacological interventions [121] [132], and is considered easy to use and understand. However, 11 % of patients do not understand the instructions for its use [81].

*Numerical and verbal rating scales –NRS and VRS*

Numerical and verbal rating scales are often used alternatively and interchangeably with VAS in clinical practice. Numerical rating scales typically range from 0 to 10, representing "no pain" and "worst possible pain" respectively. Verbal rating scales, early developed and described by Keele in 1948, consist typically of 4-7 descriptors ranked from no pain to most intense pain.

Studies have shown high correlations between VAS and NRS, although the verbal rating scales did not correlate well with the others [43] [95] [121].

## Pain treatment drugs

*Opioids*

Opioids are effective analgesics which remain important for moderate-to-severe pain after surgery. However they have unfavourable side-effects such as nausea/vomiting, constipation, pruritus, sedation and respiratory depression. Opioid receptors mediate the effect of opioids. At least three different receptors, designated μ (mu), δ (delta) and κ (kappa), are known [35]. Endogenous opioids with different preferences for these receptors are also known [124]. How endogenous inhibition of nociceptive transmission affects postoperative pain has been elucidated [165]. Opioid receptors are located peripherally and in the spinal cord. Peripheral receptors are "silent" until activated by inflammatory substances. Under such conditions, peripheral effects of opioids have been demonstrated [159] [7]. There is great loss of opioid receptors in the spinal cord after nerve section, which probably indicates a reduction in functional opioid receptors even after less severe nerve injuries/neuropathies [36]. Almost all clinically-used opioid drugs are μ agonists, i.e. selective for the μ receptor, and act at many sites in the peripheral and central nervous systems. The only opioid antagonist for human use is naloxone, which has high affinity to the μ receptor.

The most commonly-used opioids in postoperative pain treatment in Sweden are morphine and ketobemidone. Morphine acts as a main substance and also through an active metabolite, morphine- 6-glucuronide, which can accumulate and enhance opioid effects in patients with renal disturbances. Ketobemidone is an opioid agonist with similar effect and pharmacokinetic properties to those of morphine but without known active metabolites.
Morphine and ketobemidone have been considered to have equianalgetic effects [68].

Some important pharmacokinetic properties that differ among opioids are the delay between administration and effect and the duration of the effect –important for optimal opioid use in clinical practice. Upton et al examined these issues to compare opioids and routes of administrations. They defined the "relative onset" and the "relative duration" as the time the relative CNS concentration first rose to 80% of maximum and the length of time the concentration was above 80%, respectively. For an intravenous bolus dose, the relative onset varies from 1 minute for alfentanil to 6 minutes for morphine, while the relative durations are approximately 2 and 96 minutes respectively [168].

Traditionally, opioids have been administered as fixed doses at 4-6-hour intervals, with often ineffective results [48]. The use of patient-controlled analgesia (PCA) with intravenous opioids, however, has provided knowledge of individual variety in dosage requirements. Titration with or without pumps, in the hands of trained personnel, can improve analgesia in many patients [99].

*NSAID and Paracetamol*

Since Kolbe synthesized salicylic acid in 1874 as an antipyretic agent, interest in antipyretic therapy has resulted in the discovery of the analgesic and antipyretic drugs aspirin and paracetamol, still in use [16]. Little was known about the mode of action of these drugs until Vane and co-workers in 1971 reported on the inhibition of prostaglandin synthesis as a mechanism of action of aspirin drugs [171]. This however did not explain why aspirins and their pharmacological acidic relatives the non-steroid anti-inflammatory drugs (NSAIDs) had anti-inflammatory and analgesic effects while the non-acidic drug acetaminophen (paracetamol) had analgesic effect only. It was speculated that the drug distribution in the human body due to protein-binding properties and degree of acidity played a role. Acetaminophen with its almost neutral pH-value and low plasma-protein-binding ability disperses almost homogeneously while NSAIDs show a specific distribution pattern.

NSAIDs disperse in blood, liver, spleen and bone marrow. Due to their acidity they tend to accumulate in acid milieus as inflamed tissue, upper gastrointestinal tract and kidneys [51]. They reach enough concentration to inhibit the enzymes responsible for prostaglandin synthesis, namely cyclo-oxygenase-1 (COX-1) and its isoform COX-2. COX-1 is important in regulating normal cellular processes such as maintenance of normal renal and platelet function and gastrointestinal mucosa; while the expression of COX-2 is increased mainly during states of inflammation but is usually not detectible in most tissues [38]. NSAIDs inhibit the activity of both enzymes but their clinical effectiveness is believed to be due to the effects on COX-2 [152]. By inhibiting

prostaglandin-mediated mechanisms, NSAIDs can reduce pain and peripheral sensitisation [78]. Prostaglandins acting in the central nervous system (CNS) to produce hyperalgesia can also be accessible for inhibition by NSAIDs [60].

Some data suggest that the acute analgesic effect of NSAIDs results from suppression of a nociceptive process, independently of the prostaglandin inhibition, both peripherally [57] and in the CNS [67 107]. Besides, NSAIDs may also potentiate the anti-nociceptive action of opioids [90 105]. The major side-effects of NSAIDs are well-documented and include inhibition of platelet function [118] a wide range of gastrointestinal problems [144 182] and increased risk of anaphylaxis in patients with asthma and allergic rhinitis [14] and effects on renal function [175].

Specific COX-2 inhibitors have been developed which are as effective in pain relief as traditional NSAIDs without affecting platelet aggregation or gastrointestinal mucosa. Regarding renal effects, however, their role is unclear [152]. Long-term safety studies however, have revealed serious cardiovascular events, and this has raised the question of the safety and superiority of COX-2 inhibitors. More research has been called for.

The mechanisms of the antipyretic and analgesic effects of paracetamol are unknown, but inhibition of cyclo-oxygenase products has been discussed [94]. Its major advantage is the relative absence of side- effects in recommended doses, and it is used as a basic analgesic in acute and postoperative pain states.

NSAIDs and paracetamol both play an important role in balanced postoperative pain treatment: together and individually they result in opioid-sparing and improved analgesia [62 66 140 141]. A recent review elucidates new insights into the mechanisms of action of paracetamol in its role as a complementary drug in opioid-sparing analgesia [139].

*Local anaesthetics*

Local anaesthetics are generally well tolerated. They are indicated for various types of surgical anaesthesia and postoperative pain management. Long-acting anaesthetics are preferred for postoperative analgesia and bupivacaine, with the longest duration, has conventionally been widely used, although it is associated with greater cardiotoxicity than shorter-acting agents are. Serious cardiovascular and CNS complications have been reported with bupivacaine [5 58 88]. When developing its isomer levobupivacaine, an agent was aimed at that would have lower toxicity but equal efficacy and nerve block properties. The onset of action is ≤ 15 minutes and the duration of sensory block varies with way of administration but is similar to, or tends to be longer than, that of bupivacaine [49]. Cardiovascular and CNS effects of levobupivacaine are reportedly less than those of bupivacaine [53].

## Multimodal pain treatment

Increased understanding of the patho-physiology of pain has led to a combination analgesic approach to postoperative pain treatment. This balanced or multimodal pain treatment was introduced over ten years ago [75] to take advantage of additive and synergistic effects by combining different analgesics and sites of administration. The concept is opioid-sparing [46 103 56] and gives increased pain relief, even in mobilisation [125 153]. Data to show whether it reduces adverse opioid-related side-effects have so far been limited, but a recent meta-analysis shows nausea and sedation significantly reduced by approximately 30% [104].

The concept of balanced analgesia, dynamic pain relief, integrated rehabilitation programme and its effects on outcome are important topics for future study [73].

## Post-operative pain management

*Guidelines and organisation*

Providing adequate pain treatment after surgery is a central task for caregivers of surgical patients, motivated above all on fundamental humanitarian grounds: "By any reasonable code, freedom from pain should be a basic human right, limited only by our knowledge to achieve it." [89] Secondary aims are reduced morbidity and mortality, reduced surgical stress response, improved recovery and economic benefits.

Official guidelines for the management of postoperative pain were first published in Australia, in 1988 [30]. These and subsequent guidelines [3 1] from other countries and international organisations [2] have recommended the establishment of institutional teams to administer pain management. As a consequence, Acute Pain Services (APS) have been developed in hospitals in many countries. The first APSs were introduced in the United States [138] and in Germany [127]. In the early 1990s the number of hospitals with an APS significantly increased [180 135 111]. The structure differs among hospitals due to national recommendations, local conditions and different opinions on quality criteria [157]. Rawal lists the main components of a "good APS": designated personnel on duty round the clock, regular pain assessment with appropriate scales at rest and on movement, documentation, preset goals regarding maximum pain score levels as well as mobilisation and rehabilitation, active cooperation with surgeons and ward nurses, ongoing teaching programmes for ward nurses, patient education and regular audits of analgesic techniques and cost-effectiveness [134].

A survey including 2,383 patients observed a major improvement in pain scores after APS inception and there is evidence that good pain control reduces

morbidity and facilitates return to normal function after surgical trauma[12a]. A decline in pneumonia, cardiovascular, gastrointestinal and thromboembolic problems has been shown [12] [139a].The negative consequences of surgical stress response can be reduced [74]. Surgical stress response involves endocrinal-metabolic changes triggered by the surgical trauma and pain, and can affect postoperative morbidity and mortality. Recent research has even suggested that good pain control lessens the risk of chronic pain [126] [100] [71] [76] [42].

A recent trial including 1,975 surgical inpatients analysed an acute pain service and found it cost-effective [156] However, economic consequences of pain control are difficult to demonstrate [77] [174]. Nevertheless, the demand will probably increase. This may require us to combine good ideas and evidence-based suggestions. Better staff education, surgeons' active co-operation with pain management teams, surgery-specific pain treatment and rehabilitation programmes, clear responsibility and commitment areas, pain management after day-care surgery and improved compliance by ward nurses in APS goals have been suggested [134] [15]. A more appropriate organisation could possibly include all these. A well-functioning APS should provide an organisational framework for an appropriate level of care in acute and postoperative pain. Its role of ensuring safety in methods of treatment, and its commitment to audits and clinical research into efficacy and outcome, are very important [174].

*The PCA method*

In patient-controlled analgesia (PCA), the patient is in control of his or her own pain medication. In hospitalised patients the term most commonly refers to intravenous opioid use. Whenever needed, the patient can press a button and via an electronic device receive a small amount of the drug.

The PCA system was developed in response to the under-treatment of pain in numerous hospital patients. In 1968 Sechzer investigated the analgesic efficacy and opioid requirement after small intravenous doses of opioids given by a nurse on patients' demand. Sechzer reported considerable variation in opioid requirement between patients, but a relatively consistent individual need [147]. In the late 1960s, instruments for self-administration of analgesics were invented [72] and Sechzer described his initial experience of the PCA system as a highly satisfactory method for treating postoperative pain [148].

Numerous investigations have since confirmed the conclusion that postoperative PCA provides higher patient satisfaction than traditional nurse-administered analgesia, and that caregivers' expectations of the method have grown [11].

Diverse advantages have been attributed to the PCA method. Some of these are less pain in hospital but also after discharge, earlier normalisation of ventilation and body temperature [85], earlier ambulation, reduced need for postoperative antibiotics, earlier introduction of solid food, lower incidence of ileus and shorter hospital stay [172]. These findings however have been unconfirmed or refuted by other investigators. Rational explanations of the benefits are often lacking but several reasons have been suggested such as altered metabolic response due to better matching of opioids to patients' needs, and the avoidance of high morphine peaks [172]. Egan suggests that a sense of "control" over pain could result in well-being and positive patient reporting [40].

Regarding pain treatment efficacy, opioid consumption and reduction in side-effects, results diverge. Positive effects on cardiopulmonary or thromboembolic complications or hospital stay have not been consistently proved; nor have meta-analyses and reviews produced convincing proofs of the efficacy of PCA. [11 87 97 169].

Consequently, many authors have suggested improvements to the method, hypothesising that the flexibility in opioid delivery it allows is not fully utilised: individualised doses and intervals would improve both efficacy and safety [45 86 97 176]. The need for trained personnel, medical supervision and patient selection and information have been repeatedly emphasised [27 45 87 137 177].

The different suggestions have been investigated with diverse results. Dose adjustments did not result in improvements [92], while patient education has been investigated and found beneficial by some authors [45] but without effect by others [52 84].

All-in-all, it has been difficult to demonstrate scientific evidence for improved outcomes with PCA. There is however evidence that patients prefer PCA, and "that PCA with opioids is slightly more analgesic than conventional opioid analgesia" [169].

Lehman however considers that the most important lesson from PCA is the insight that pain thresholds and tolerance vary widely and are unpredictable in individual patients. Both subjective thresholds and 'objective' parameters such as therapeutic plasma drug concentrations vary greatly [163]. Together with the knowledge that patients expect immediate help when their individual pain threshold is crossed [79], the lesson from PCA use constitutes the "PCA principle". This "involves trusting the patient, providing adequate monitoring and appropriate documentation, and of course, raising the educational level of the staff on surgical wards". The PCA principle can encourage improvements in conventional pain management: the method can be applied even where the requisite pumps are not available [87].

Despite lack of evidence of its effect on outcome, we can conclude that the use of PCA has opened our eyes to the large individual variation in opioid need. This in turn has led to changed opioid therapy routines and improved pain management.

## Persistent post-surgical pain

The problem of long-lasting pain after surgery was earlier revealed in a survey of pain clinics in Scotland. Twenty percent of the patients studied identified surgery as one cause, or the sole cause of their persistent pain [34]. One recent investigation showed 46% of long-lasting pain originating from medical procedures [179].

Criteria for defining persistent post-surgical pain have subsequently been worked out [101]:

- The pain should have developed after a surgical procedure
- The pain should be of at least two months duration
- Other causes of the pain should have been excluded
- The possibility that the pain stems a pre-existing problem must be explored and exclusion attempted.

(The authors emphasise that there is a "grey area" here, as pain can be exacerbated by surgery but the possibility of natural impairment cannot be ruled out.)

Investigators have defined post-mastectomy pain in different ways based on the character, location and timing of the onset [173] of the pain. One author studying the epidemiology of post-mastectomy pain syndrome [155] included only patients with typically neuropathic pain which had persisted for over three months. Forty-three percent of a total of 408 patients reported such pain. Another author investigating pain 2-6 years after surgery found 53% with long term pain (LTP) after mastectomy with breast reconstruction [170].

Chronic pain is common after various kinds of surgery. Best documented is pain after limb amputation, inguinal hernia repair, breast surgery, cholecystectomy and thoracic surgery. Predictive factors related to surgery are pre-, intra- and postoperative, and include pre- and postoperative pain, surgical approach, repeat surgery, radiation therapy to area, and psychological vulnerability, depression and anxiety [126].

Certain patient groups run greater risks of developing chronic post-surgical pain. Examples mentioned are Raynaud's disease, migraine, fibromyalgia and familial and psychological factors [9 10]. Changes in the nervous system could underlie some of these syndromes; but inherent neural plasticity resulting in amplification of sensory input [25] could "well have a bearing on chronic post-surgical pain." [100].

# Aims

The general aim was to study postoperative pain treatment strategies for reduced pain and opioid consumption in patients suffering moderate-to-severe postoperative pain.

The specific aims were to:

- investigate the efficacy of PCA and nurse-administered opioid treatment after breast cancer surgery,
- investigate pain intensity and opioid requirement in postoperative pain patients treated with NSAID as an adjuvant to opioids and paracetamol,
- investigate pain intensity and opioid requirement in postoperative pain patients treated with a local anaesthetic as an adjuvant to opioids and paracetamol,
- evaluate side effects in patients treated for postoperative pain in the project,
- evaluate the prevalence of long term remaining pain in patients after breast cancer surgery.

# METHODS

In the present work post-surgical pain and analgesic consumption were studied in women after breast cancer surgery and caesarean section performed at Karolinska University Hospital in 1996 – 2005.

All the studies were performed at Karolinska University Hospital, Stockholm and were approved by the hospital's Ethics Committee.

**Characteristics of the four studies**

| Year of publication | Paper I<br>2002 | Paper II<br>2000 | Paper III<br>2005 | Paper IV<br>manuscript |
|---|---|---|---|---|
| Study design | Prospective randomised Follow-up-questionnaire | Prospective randomised placebo-controlled double-blind | Prospective randomised placebo-controlled double-blind | Prospective randomised placebo-controlled double-blind |
| Study period | 1996 – 1997+ 2000 | 1997 – 1998 | 1999 – 2001 | 2003 – 2006 |
| Number of subjects | 144 | 50 | 48 | 43 |
| Patient category | Women after breast cancer surgery | Women after caesarean section | Women after IBR with implants | Women after DBR with implants |
| Observation period | 24 hours (3-4 years) | 24 hours | 64 hours | 45 hours |
| Method of analgesia | Opioid PCA / NA | Diclofenac / Placebo<br>Opioid PCA | Diclofenac / Placebo<br>Opioid PCA | L a / Placebo<br>Opioid PCA |
| Variables | Pain at rest<br>Opioid consumption<br>Hospital stay<br>Long-term remaining pain | Pain at rest<br>Opioid consumption<br>Nausea | Pain at rest and on movement<br>Opioid consumption<br>Nausea<br>Tiredness<br>Bleeding | Pain at rest and on movement<br>Opioid consumption<br>Nausea<br>Hospital stay<br>Infection frequency |

## Patients

All the patients understood and spoke the Swedish language. They gave their verbal informed consent to inclusion in the study.

In the four studies 293 women listed for breast surgery or caesarean section were included. Eight patients were excluded. In study I five patients were excluded, four due to incomplete protocols and one at her own request. In study III two patients were excluded, one because of probable renal disease and one at her own request. In study IV one patient were excluded due to changed type of surgery.

## Randomisation

In study I randomisation to either of two treatment groups was performed by patient's date of birth. In studies II – IV suppositories and ampoules were blinded and packed by the hospital pharmacy according to a computer-created table.

## General anaesthesia

All the patients in studies I, III and IV received general anaesthesia induced with either thiopenthone (4 mg/kg) or propfol (1.5-2.5 mg/kg) maintained with isoflurane and fentanyl (0.05-0.2 mg). In studies I and III a supplementary single dose of atracurium or pancuronium was given before tracheal intubation. In study IV larynx-masks were used instead of tracheal intubation. All the patients received local anaesthesia with lidocaine 100-250 mg infiltrated in the surgical area after induction of anaesthesia but prior to surgery.

## Opioids

In study I morphine was the drug of choice although a few patients received ketobemidone. In study II all patients received ketobemidone. In studies III and IV all but five patients received morphine. The drugs were considered equipotent. Opioid consumption was recorded continuously during the study periods but was reported for different time intervals.

## Paracetamol

Oral Paracetamol 1 g x 4 initiated one hour before surgery was given to all patients in studies III and IV.

## Patient-controlled analgesia (PCA)

In the patient-controlled analgesia used in all four studies the drug was delivered to the patients through an ABBOTT PCA device connected to an intravenous line. Bolus doses could be administered at an amount of 1 mg on demand in studies I and II but the doses were 2 mg in studies III and IV. Lock-out time was six minutes in all the studies. PCA was started immediately after the patient's arrival at the post-operative unit in studies II - IV. In study I, the patients received nurse-administered opioids for

the three first postoperative hours due to presumed post-anaesthetic tiredness. The time the PCA devices were kept was decided by each patient's needs in all the studies.

## Nurse-administered analgesia (NA)

The opioid was given intravenously by a nurse in titrated doses of 2.5 – 7.5 mg according to the patient's needs, Study I

## Rescue analgesia

A nurse could titrate extra doses of opioids if needed in studies I - III. In study IV 40 mg of parecoxib (Dynastat®) was used as rescue analgesic. Time to patients' demand for rescue medication in study IV was measured.

## Pain assessment

In the four studies pain intensity was measured using a visual analogue scale (VAS), which was a 10 cm horizontal line with end points marked as "no pain at all" and "worst pain imaginable". Pain was measured at rest in studies I - II and at rest and during mobilisation achieved by raising the arm on the operated side and crossing it to the other side of the body in studies III and IV.

## Surgery

*Breast surgery*
Four different surgical procedures were performed as described in study I. The techniques for immediate and delayed reconstruction are likewise described in study III. In study IV the technique for dissection of the submuscular pocket differed among surgeons. This was not specifically studied with regard to postoperative pain in this project.

*Caesarean section*
The elective sections were performed after 38 full gestational weeks. Indications for the operation were cephalopelvic disproportion, breech position or repeat sections.

## PCA/NA after breast cancer surgery –Study I

The 149 patients included were scheduled for breast cancer surgery.

After randomisation into the main groups PCA and NA, the subjects were divided into four sub-groups with respect to type of surgery:

| | |
|---|---|
| M | Mastectomy |
| ML | Mastectomy and axillary lymph-node dissection |
| MR | Mastectomy and reconstruction using submuscular implants |
| MRL | Mastectomy, reconstruction using submuscular implants and axillary lymph node dissection |

Pain was assessed every thirty minutes during the first three post-operative hours and thereafter every third hour for a total

of 24 hours, and opioid consumption was recorded.

## NSAID as adjuvant –Studies II and III

Study II
Fifty healthy women with uncomplicated pregnancy were included. The caesarean section was done at the end of 38 full gestational weeks. The indications for operation were cephalopelvic disproportions, breech position or repeat sections. All these patients were anaesthetised with spinal block. The subarachnoid injection was performed with a 27-gauge Whitacre spinal needle in the L3-L4 interspace, with the parturient in sitting position. The block dose was 12.5 mg 0.5% bupivacaine (2.5 ml hyperbaric solution with 8% glucose). A block level of T4 was aimed at before start of surgery.

All the patients received "blinded" suppositories of either 50 mg diclofenac or placebo every eighth hour for 24 hours, starting immediately after surgery while still on the operating table.

Pain assessments were obtained every hour during the first 12 hours and thereafter every third hour post-surgery, and opioid consumption was recorded.

Study III
Fifty women scheduled for mastectomy with IBR, with or without axillary lymph node dissection were included. The inclusion criteria were either breast cancer or a familiar disposition for breast cancer. Exclusion criteria were contraindications for NSAID. All these patients had a wound drain placed in the operated area of the reconstructed breast. After randomisation into either the diclofenac or placebo group, the subjects were divided into subgroups according to whether axillary lymph node dissection (ALND) was performed. All the patients received general anaesthesia and infiltration of lidocaine before skin incision as in study I.

All the patients received "blinded" suppositories of either 50 mg diclofenac or placebo every eighth hour for three days, starting one hour before surgery.

Pain at rest and on movement was assessed every hour during the first six post-operative hours and thereafter every fourth hour. Opioid consumption was recorded.

According to the routines at the time, all the patients were given low-molecular-weight heparin 20 mg subcutaneously every 24 hours, starting approximately one hour before surgery.

## Local anaesthetic as adjuvant –Study IV

Forty-four women undergoing secondary breast reconstruction were included. Inclusion criteria were unilateral breast reconstruction with or without contralateral reduction, or in two cases augmentation mammaplasty. All the patients had a wound drain placed in the operated area of the reconstructed breast.

Immediately after incision closure the patients received either levobupivacaine (Chirocaine®) 2.5 mg/ml or normal saline 15 ml via a 16 G Portex epidural catheter left in place in the pocket dissected for the expander prosthesis. The study-solution was subsequently instilled in a double-blind manner every three h for 45 hours whereupon the catheter was removed.

Where breast reduction mammaplasty was performed in the contralateral breast, an indwelling catheter was placed in that wound site too. Then 10 ml of bupivacaine 2.5 mg/ml was similarly instilled after wound closure and thereafter ropivacaine 2 mg/ml 10 ml every 3 h, aiming at pain relief in the breast that would not be assessed in the study investigation. However, this contralateral catheter procedure was not performed where the operation was too small to justify a wound drainage, which was the case in 12 patients.

Pain at rest and on movement was assessed every hour of the first six hours after surgery, thereafter every three hours, and the patients were requested to assess the pain intensity in the reconstructed breast. Measurements were made before and 30 minutes after local anaesthesia instillation. During these thirty minutes the wound drainage was held closed.

Information on morphine requirement, irradiation therapy, occurrence of infection and hospital stay were obtained from the patients' medical records.

## Side effects –Studies II-IV

*Nausea and tiredness evaluation*
Nausea and vomiting were noted (study II).

Nausea and tiredness assessments were obtained every hour during the first six post-operative hours and thereafter every fourth hour using a visual analogue scale marked "no nausea" and "vomiting" or "no tiredness" and "sleeping" at the end points (study III).

Patients were questioned about nausea and vomiting every hour for the first six post-operative hours and thereafter every third hour during the observation period (study IV).

*Bleeding assessments*
One wound drain was placed in the submuscular pocket and in case of ALND

another in the axilla. The drains were kept in place until the volume of blood and secretion in the reservoirs was less than 50 ml/24 h. Intra-operative bleeding was estimated from increased weight of towels and added to postoperative bleeding measured in millilitres from the drain reservoirs (study III).

*Infection frequency*
The occurrence of infection was recorded in study IV.

*Adverse events*
Postoperative bleeding problems; development of haematomas, re-operation, respiratory depression and/or other adverse events were documented.

## Hospital stay –Studies I and IV

The patients were discharged from hospital as soon as they felt confident to do so and their medical condition allowed it. Average stay in hospital was calculated in studies I and IV.

## Prevalence of long term pain – Study I

Thirty-seven-to-fifty months following surgery, a questionnaire containing questions about possible persistent pain was sent to 118 survivors. (See enclosed Appendix).

## Statistical analyses

*Pain and opioid consumption*
Mean values of pain VAS scores for each patient were calculated for the time periods. Medians of these means were then calculated over the patients in each study group. The Mann-Whitney *U* test was used to compare the medians between the groups. When appropriate Wilcoxon´s test or Student´s *t* statistic was used to test differences between two groups. For three or more groups one- or two-way analysis of variances (ANOVA) was used.

*Nausea, tiredness, hospital stay and persistent pain*
Chi-squared statistics or the Mann-Whitney *U*-test were used to test differences in distributions between groups.

*Bleeding*
Mann-Whitney *U* tests and multivariate analyses on log-transformed values were performed.

P-value $< 0.05$ was considered significant.

# RESULTS

## Demographics –Studies I-IV

Study I
The 144 women were divided into two groups, PCA and NA. These were comparable in numbers, though there was a difference in numbers in the four subgroups. There was also a difference in age between the subgroups.

After 37 – 50 months when a follow-up investigation was made concerning long-term persistent pain, 19 women had died, three had moved abroad and four had declined further participation. The remaining 118 women were contacted, and 110 answered the questionnaire.

Study II
The 50 women were divided regarding treatment with diclofenac or placebo into two equal groups with similar demographic data.

Study III
The 48 women were equally divided regarding treatment into two groups Diclofenac/Placebo and subsequently according to whether they had ALND. However there was a difference in distribution between unilateral and bilateral operations.

Study IV
The 43 women were divided regarding treatment with levobupivacaine or placebo into two groups with similar demographic data.

## Pain intensity and opioid requirement –Study I

*Pain intensity at rest and opioid requirement*
The women in the PCA group had a significantly lower level of pain intensity ($p < 0.001$) and consumed more opioids ($p = 0.026$) during the 3-24 h postoperative period than those in the NA group 10.6 (12.6) mg and 6.2 (10.8) mg respectively (Fig. 2).

The women who underwent immediate breast reconstruction with submuscular

implants suffered more pain and required more opioids than patients not undergoing immediate reconstruction. Figure 3 illustrates how opioid intake 3-24 hours after surgery varied by method (PCA or NA) in the subgroups (Fig. 3).

During the 0-3 hours when the patients were still on the recovery ward, mean (sd) values for VAS and milligrams of nurse administered opioids were unexpectedly high in the reconstruction groups compared to the corresponding values for the other two groups: (Table 1).

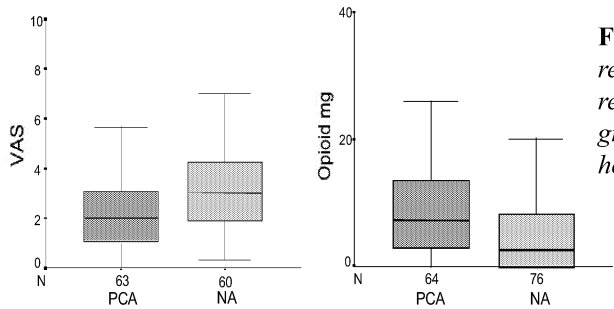


**Figure 2.** *Pain intensity at rest VAS (0-10) and opioid requirement (mg) in the main groups PCA and NA 3-24 hours post-surgery. Study 1.*

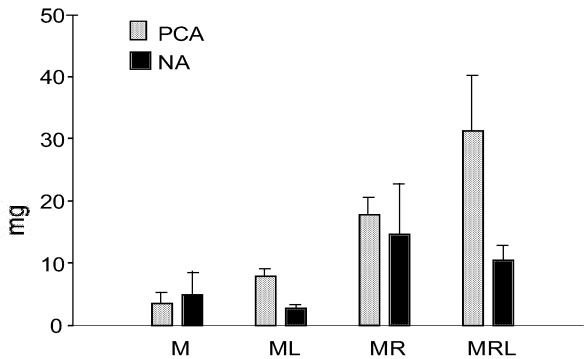


**Figure 3.** *Opioid consumption mg, mean (SE) in the sub-groups 3-24 h post-surgery. Each group divided into PCA/NA methods.Study 1.*

**Table 1.** Pain intensity and nurse-administered opioids related to surgery. 0-3 h post-operatively before division into PCA and NA groups. Study 1

| | VAS | | Opioid (mg) | |
|---|---|---|---|---|
| | n | mean (sd) | n | mean (sd) |
| M | 16 | 2.1 (1.6) | 16 | 3.2 (3.4) |
| ML | 79 | 3.0 (1.6) | 86 | 5.5 (5.2) |
| MR | 10 | **4.9** (1.2) | 12 | **11.8** (10.4) |
| MRL | 26 | **5.0** (1.1) | 27 | **12.8** (8.7) |

## Pain intensity and opioid requirement –Studies II and III

Study II

The women in the diclofenac group reported significantly less pain during the first three hours after surgery than the women in the placebo group did ($p = 0.025$). Total ketobemidone after 12 hours was 39% less in the diclofenac group than in the placebo group: means (sd) 35.8 (9.86) mg and 22 (12.38) mg respectively ($p < 0.001$) (Fig 4).

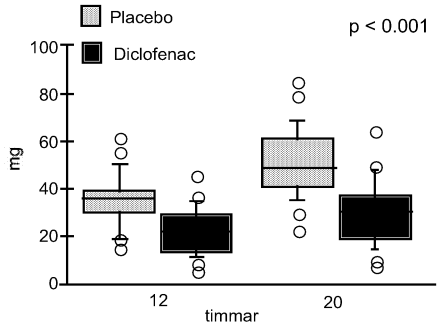


**Figure 4.** *Dose of Ketobemidone (mg) administered via PCA 12 and 20 h after caesarean section. Study II*

Study III

During the first 20 hours post-surgery, women who received diclofenac experienced significantly less pain when resting than those who received placebo ($p = 0.006$). The variation in pain intensity in the two groups during the six immediate post-operative hours is illustrated ($p = 0.002$) (Fig 5). During mobilisation, estimated differences in pain showing less pain following diclofenac administration were noted. These differences were not statistically significant. There was 34% less opioid intake in the diclofenac group than in the placebo group during the first six hours after surgery, with means (sd) of 16.9 (10.3) mg and 25.6 (10.2) mg respectively ($p = 0.007$). Over 0-20 hours the difference was 25% ($p = 0.066$). After 20 hours there was no significant

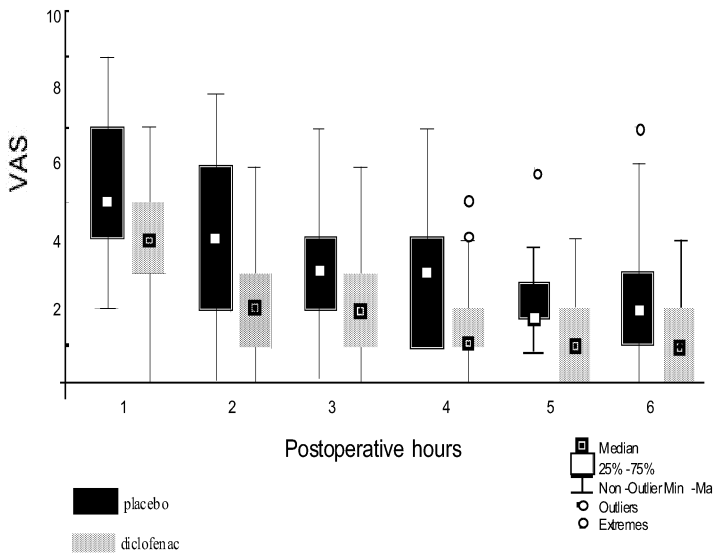


**Figure 5.** *Pain intensity at rest 0- 6 h after surgery in the treatment groups Diclofenac/ Placebo. Study III*

difference in opioid consumption between the groups.

Indvidual pain intensity during the first post-operative hour is illustrated . (Fig. 6).

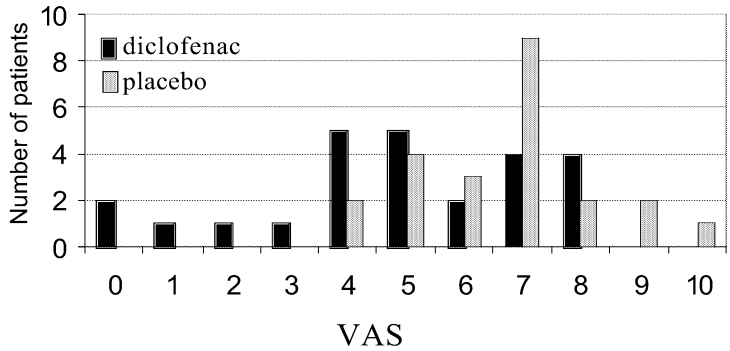


*Figure 6. Individual VAS scores for pain intensity at rest in the first hour after IBR. Study III*

## Pain intensity and opioid requirement –Study IV

The women in the levobupivacaine group reported significantly lower pain intensity at rest during the first 15 hours after surgery ($p < 0.05$) (Fig 7). On movement, the pain intensity was lower for the first six hours ($p = 0.01$) and for the time interval 18-24 hours ($p = 0.045$) (Fig 8). Total mean (sd) opioid consumption in the levobupivacaine group and in the placebo group was 24.6 (22.88) mg and 33.8 (30.82) mg respectively ($p = 0.283$).

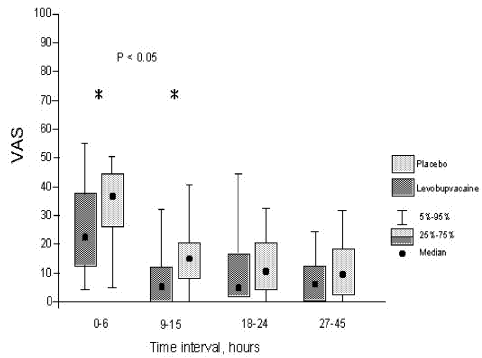


**Figure 7.** *Pain intensity (VAS) at rest at different time intervals after DBR. Study IV*

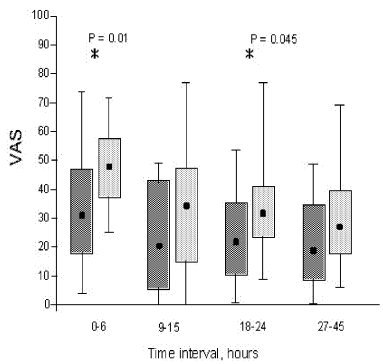


**Figure 8.** *Pain intensity (VAS) during movement at different time intervals after DBR. Study IV*

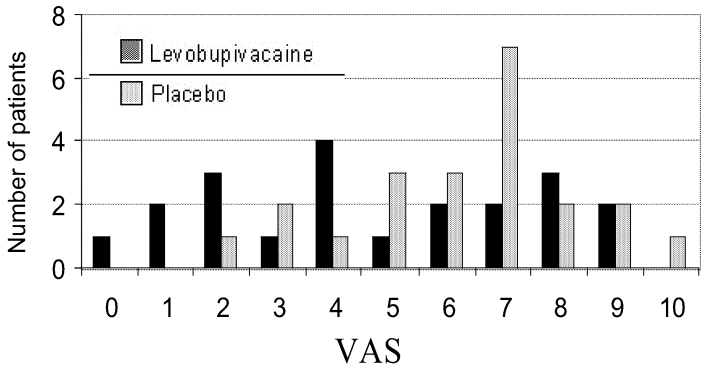


**Figure 9.** *Individual VAS scores for pain intensity at rest in the first hour after DBR. Study IV*

Pain intensity during the first post-operative hour is illustrated in (Fig. 9)

Intravenous injection of parecoxib (Dynastat®) was requested by three patients in the levobupivacine group after six, 16 and 22 hours and by four patients in the placebo group after seven, 15, 21 and 21 hours.

## Side-effects –Studies II-IV

*Nausea and tiredness*

There were no statistical differences between the groups regarding nausea and tiredness.

Study II

Nausea was experienced by 4/25 patients in the diclofenac group and by 7/25 in the placebo group.

Study III

The proportion of patients suffering nausea > 4 (VAS) at least once during the study period was 14/25 in the diclofenac group and 12/23 in the placebo group.

Study IV

Nausea in the levobupivacaine group occurred in 13/21 patients during the first postoperative day and in 7/20 on the second day. Medical treatment for nausea was given to eight patients. Corresponding, not significantly different, data for the placebo group were: 17/22, 4/18 and 14. Four women described sudden intense nausea and vomiting shortly after wound catheter injection. Two of these patients received levobupivacaine and two received placebo.

*Bleeding*

Study III

Post- but not per-operative bleeding was significantly greater with diclofenac than with placebo ($p < 0.01$). This difference was more pronounced in the patients with ALND than in those without (Fig. 10). Two patients in the diclofenac group received blood transfusion but no

patient was re-operated for haematoma or bleeding.

*Infection frequency*
Study IV
Two patients in the levobupivacaine group developed signs of infection postoperatively in the reconstructed breast and were treated with antibiotics over two weeks.

*Adverse event*
Study III
One incident of hypoventilation (respiratory rate < 6 breaths/min) occurred in one of the patients in the placebo group.

## Hospital stay – Studies I and IV

Study I
Average length of hospital stay for both treatment groups, PCA and NA, was equal at 3.2 (sd =2.0 and 1.6) days. It differed however among the subgroups. Regarding the PCA versus NA mode of pain treatment, length of stay differed for the patients in the MRL group, where the number of days was 5.8 (1.3) and 4.2 (1.1) respectively (p = 0.002).

Study IV
Mean (sd) hospital stay in the levobupivacaine group and the placebo group was 3.2 (1.15) and 3.4 (1.12) days respectively

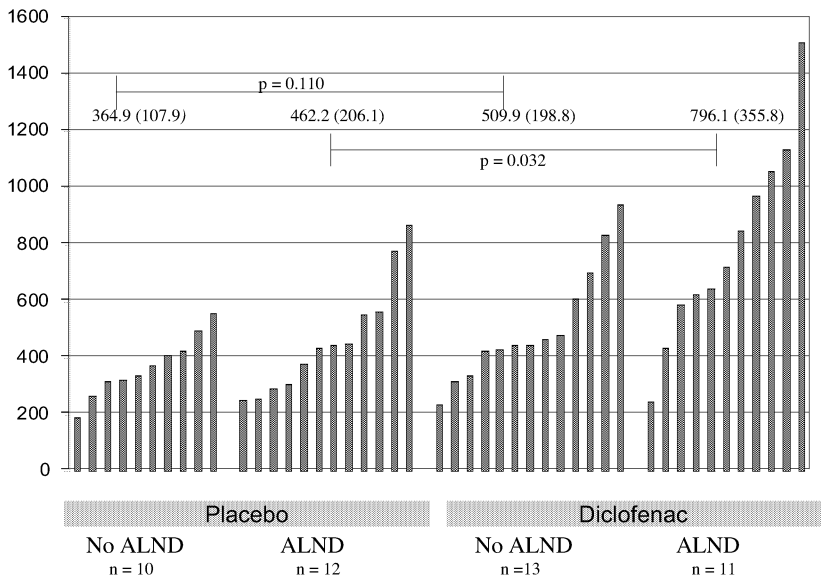


**Figure 10.** *Post-operative bleeding (ml) for each patient considering axillary lymph node dissection (ALND) and treatment. Mean (sd) and Bonferroni corrected P-values in the figure. Study III*

## Prevalence of long-term persistent pain – Study I

After 37-50 months 118 women were contacted with a questionnaire. Twenty-eight (25%) of 110 responders reported some degree of persistent pain of whom 24 had undergone ALND. These women also rated their persistent pain higher than did the four women who had no ALND (Table 2). Of the 28 positive responders 21 had belonged to the NA group and seven to the PCA group.

Table 2. Numbers of patients with long term pain (LTP) and their worst pain scores after 3-4 years (VAS 0-10 mean). Study I

| | Responders | LTP n | LTP % | VAS mean | VAS range |
|---|---|---|---|---|---|
| M | 13 | 3 | 23.1 | 3.4 | 2.5-4.8 |
| ML | 65 | 17 | 26.2 | 4.6 | 1.0-9.3 |
| MR | 10 | 1 | 10.0 | 1.0 | 1.0 |
| MRL | 22 | 7 | 31.8 | 5.2 | 2.2-9.0 |
| N | 110 | 28 | 25.4 | 4.5 | 1.0-9.3 |

# DISCUSSION

## Pain measurement and report of data

Although the VAS is very frequently used in studies, the way of handling data is somewhat problematic and much debated. The visual analogue scale is not considered equidistant and as such provides ordinal data at the most [6]. This requires non-parametric statistic calculation based on rank order, which raises difficulties in analysing and comparing data from groups. On the other hand, these shortcomings reflect rather the problematic nature of the pain variable as such, with its inherent difficulty to be measured and compared among groups.

However, some authors insist that the VAS *is* linear and has "ratio scale properties", and can be used as an interval scale with respect to statistical calculations. [115 116 130 132].

The limitation of using unidimensional methods for measuring multidimensional pain has been pointed out by many authors [24 81]. Clark's study demonstrated that patients' pain ratings on a numerical rating scale (NRS) were determined more by their emotional state than by their experienced sensory pain.

## PCA and on-demand nurse administration –Study I

Adequate pain control after surgery is important for improving patient's well-being but also for reducing morbidity and facilitating recovery. Breast-cancer surgery is frequently associated with postoperative pain and pain-induced restriction of movement. The facts that acute and long-term pain may be related and that the prevalence of long-term pain after breast cancer surgery is reportedly 15-53% in studies [129 167 170] performed after 1990 also make it an issue of great interest.

In our first study we compared PCA and conventional analgesia in women after breast cancer surgery and found that those treated with PCA had better pain relief. The many reviews on the subject have failed to establish clear evidence for the superiority of PCA regarding analgesic efficacy [11 97 169].

However, the lower pain intensity for our PCA patients undergoing different types of breast surgery indicates that the patients *did* benefit from the opioids they administered themselves. Perhaps this was because they matched and titrated their doses to varying pain intensity. In the NA group the poorer result was probably affected by nurses' lower compliance with the patients' needs. On the other hand the women in our study who underwent breast reconstruction, despite nearly three times higher opioid consumption during the first three postoperative hours, did not attain the same level of pain relief as those who did not undergo reconstruction (Table 1). These women's pain may have been less opioid-sensitive and thus they were unable to reach better pain relief with the opioid drug available.

However, the higher opioid consumption in our PCA group cannot be explained by opioids being ineffective in the reconstruction groups; in the largest group, the ML group (no reconstruction), the PCA patients similarly consumed more opioids than those conventionally treated. On the contrary the patients in the M group (the less extensive operations) consumed less opioids than those whose opioids were administered by a nurse. This subgroup is relatively small, which makes the results too uncertain for conclusions. However, there are indications in the literature that nurses tend to overestimate patients' slight pain and underestimate severe pain [154 185]. One interpretation of these findings is that when nurses underestimate, their main focus is on action, and sometimes they know they "have no time to act, or feel inadequate on how to act" [64].

Higher, lower and similar opioid intakes with PCA compared to traditional intravenous pain treatment are reported in the literature [28 85 23]. This inconsistency may relate to the extremely large variability in individual consumption among patients who self-administer opioids [87].

Opioid requirements and therapeutic plasma concentrations have been investigated by Tamsen et al. in a series of studies. They showed that analgesic requirements and hence therapeutic concentrations vary widely (four- to six-fold) but that patients can maintain a relatively constant plasma level of opioids when allowed to administer the drug themselves during the postoperative period. Minimal effective opioid concentrations also differ between patients, and individual endorphin levels in cerebral fluid affect the requirement for opioid analgesics [33 64 162-164].

The great variety in opioid requirements demonstrated in our four subgroups (study I, Fig.4) could certainly be explained by the varied extent of the surgical procedures, generating as they did differing postoperative pain intensities.

Developments in hospital organisation for postoperative pain management when we were collecting data can also have influenced the results of opioid consumption in study I somewhat. The nurses on the surgical wards had been trained in intravenous opioid titration and PCA technique. Quality criteria for pain treatment in the hospital had been formulated. Pain should be made visible, i.e. measured and documented, and a maximum pain score of 4/10 was stated for the postoperative period. These stipulated changes can have led to postoperative-care nurses being more generous with opioids thanks to good monitoring and staffing, while ward nurses remained cautious and somewhat restrictive due to a lower level of such security precautions. This resulted in initially high doses of opioids for women after breast reconstruction – and the opportunity for our investigation to identify their unique pain situation!

Some authors believe that patients are prepared to tolerate some pain as long as they feel that immediate pain relief is at hand, thus keeping drug consumption low enough to avoid unpleasant side-effects [87]. A prerequisite for this however, ought to be effectiveness of the available drug in alleviating the patient's pain. This may not have been the case in our reconstruction patients. The large opioid demand in these groups was likely due to the patients' efforts to obtain relief from pain that was only partially opioid-sensitive. This makes opioid-PCA as a sole pain treatment method questionable or even inappropriate after immediate breast-reconstruction.

## NSAID as adjuvant –Studies II and III

In studies II and III in this project we evaluated NSAID (diclofenac) as an additional analgesic to opioid alone or to opioid and paracetamol. The two patient categories were women after caesarean section and women after immediate breast reconstruction (IBR). Both would benefit from opioids postoperatively, limited so as not to reach a level producing side-effects.

Pain from uterine contractions is poorly responsive to opioids [122]. Also, new-born infants are affected negatively by opioids given to the mother [133]. Depressed neurobehavioural scores in neonates were found due to accumulation of opioids and their metabolites in breast milk, when opioids were given after partus via intravenous PCA technique [181]. Such effects might also disturb the interaction between mother and child and negatively affect the infant's feeding behaviour during the first few days [119].

In study I we found it difficult to reach satisfying pain relief using opioid analgesia in women after breast reconstruction. This can indicate a less opioid-sensitive pain component in these patients' pain as well. We also observed hypoventilation in patients (out of the

trial) after IBR due to increasing doses of opioids without successful pain relief. Thus we found it reasonable to evaluate a combination of diclofenac and opioids in these patient categories, in a study aiming at good pain relief and reduced opioid requirement in the primary postoperative period.

Our results from studies II and III indicate that adding diclofenac to opioid treatment with or without paracetamol improves pain relief in the first postoperative hours at rest, and reduces the need for opioids after caesarean section and immediate breast reconstruction. This is in line with the results of others [140].

Treatment with paracetamol and NSAID is often started before surgery [19 32]. After caesarean section however NSAIDs cannot be used before delivery due to the potential risk of premature closure of the ductus arteriosus, or foetal pulmonary hypertension [178]. After IBR in study III we started the additional oral diclofenac treatment one hour before surgery and although we reached statistical differences in pain relief in the first postoperative hours, we cannot be fully satisfied with the result. Overall pain scores were high after IBR and 15/25, 60% of the diclofenac-treated patients still reported ≥ 5 on the VAS in the first postoperative hour. For those receiving placebo the corresponding figures were 21/23, 91%.

Pain on movement was not assessed in the caesarean section study (study II) but the breast-reconstructed patients (study III) did not reach satisfactory pain relief during movement with additional diclofenac. Although movement pain is not investigated in most studies, it is important to treat this so as to achieve improved rehabilitation and early discharge. Many of our patients complained of movement pain and discomfort from the axillae drains.

## Local anaesthetic as adjuvant –Study IV

Local anaesthesia with different routes of administration improves analgesia in the early postoperative period:

Infiltrated before incision, local anaesthesia reduces pain in the first few hours after breast reduction [114 142].

Irrigated into open wounds local anaesthesia can be effective in relieving pain and lengthening the pain-free period after surgery [31 113]. This has also been shown after augmentation mammaplasty [102].

Administered post-operatively through catheters, long-acting local anaesthetics have been used in various surgical specialities, where they improve pain relief and diminish opioid consumption [54 55].

As the foregoing has not been evaluated after breast reconstruction in breast-cancer-operated patients, we evaluated levobupivacaine intermittently injected in the operated site starting on wound closure.

Although we did attain improved pain relief, many patients rated pain as unacceptably high during the first few postoperative hours. In our experience it is common that many breast-reconstructed patients feel intensive pain soon after or immediately on awakening after general anaesthesia, despite paracetamol given before surgery and an opioid supply during surgery. This was confirmed in our study IV were 77% of the women in the placebo group scored 47-100 on the VAS. In the levobupivacaine group 48% of the women still rated between 48 and 94 on the VAS within the first postoperative hour, which cannot be considered satisfactory (Fig. 9).

This inadequate analgesia in the immediate postoperative period might be explained by insufficient dispersion of the local anaesthetic in the wound area for technical reasons such as type and/or position of the catheter. We used a Portex epidural catheter with a few holes close to the tip. Numerous holes along the catheter placed in the wound site may help spread the volume of the liquid more efficiently. On the other hand blockage of catheter holes can always occur and result in poor distribution of the local anaesthesia. Varying filling volume of the prosthesis resulting in differing skin and muscle tension is also a conceivable reason for high pain intensity in the awakening period, as are differences in operation techniques.

Wide variability in postoperative pain intensity after breast implants as we found in our study is also described in the literature [87] [123]. Pacik also reported unexpected variability in pain *location*: in five of seven consecutive patients undergoing breast reconstruction and complaining of moderate-to-severe pain after augmentation mammaplasty, the pain was located elsewhere than in the breast; substernally and/or in the armpits, ribs and shoulder blades. These findings can help to understand the aetiology of the pain as briefly discussed by the author. As we did not investigate the locality of pain, we do not know whether there was a similar variability in the location of pain following delayed breast reconstruction.

Also, surgical technique may affect postoperative pain. Submuscular dissection for the prosthesis in this trial was performed ‘sharp’, blunt or with diathermy. However, the diathermy technique was used only once; (the 57-year-old woman was allocated to the levobupivacaine group and experienced mild pain in the postoperative period). Sharp or blunt technique was used interchangeably, so the variations regarding this part of the surgery may not

have influenced our patients' experience of postoperative pain.

Continuous infusion of local anaesthesia for postoperative pain treatment has been studied quite extensively, and bupivacaine reportedly reduces average pain scores and cumulative pain medication. This has been noted after tissue expander breast reconstruction [93], after autologous breast reconstruction [13] and after axillary lymph-node dissection [146]. One study, on continuous bupivacaine via operation site catheter for 48 hours after transverse rectus abdominis muscle (TRAM) flap breast reconstruction, did not measure pain intensity but showed reduced narcotic requirement and length of hospital stay [91].

Intermittent bolus administration can be favourable, as pain varies in individuals and after different types of surgery. Patient-controlled administration has been studied in hospital and at home with good results, when patients prefer to be in control of their own pain treatment [123 134 136].

We chose an intermittent three-hour dose for 45 hours for instilling levobupivacaine/placebo. In view of the above, this schedule should probably be individually adjusted as to dose amount, intervals and catheter maintenance. After 24 hours most of our patients, but not all, experienced tolerable pain and would probably have had good pain control with oral analgesics.

However we conclude that local anaesthesia can be effective in improving pain treatment after breast reconstruction; but more studies are needed to investigate different types of wound catheter dose schedule and surgical technique.

## Side effects –Studies II-IV

*Nausea*

Despite improved analgesia and reduced opioid consumption we detected no differences in postoperative nausea. This is in line with most other clinical studies documenting opioid-saving effects. However a recent meta-analysis evaluating the risk of morphine side-effects in 22 prospective, randomised double-blind studies including 2,307 patients demonstrated a significant decrease in nausea and vomiting by 30% and in sedation by 29% in patients treated with NSAIDs combined with intravenous morphine patient-controlled analgesia [104].

*Bleeding*

As NSAIDs affect platelet function [18], we measured blood loss in study III and evaluated any complications to postoperative bleeding.

There was more postoperative bleeding, but not peroperative bleeding, with diclofenac than with placebo. Treatment, diclofenac-or-placebo and extent of surgery affected postoperative bleeding.

These conclusions of ours have been criticised. The accuracy of direct assessment of drain fluid for estimation of blood loss has been questioned [59]. This is because mean haemoglobin concentration in drain fluid after breast cancer surgery is shown to be very low in a study of McCaul [106].

The criticism is well founded: it would have been correct to analyse the concentration of haemoglobin in the collected drain fluid. Still the increase in fluid volume after treatment with NSAID in our study is surprising if it did *not* contain blood, and this needs further research. We note that the drain fluid samples analysed in the study of McCaul et al were collected on days 3 and 4 post-operatively, while we assessed the drain fluid from 0 to 64 hours after wound closure.

The use of NSAIDs pre-operatively is controversial due to their effect on bleeding time and the hypothetical risk of haematoma and possible re-operation. In our study no patient was re-operated, but two in the diclofenac group lost enough blood to need blood transfusion. We found a higher postoperative drain fluid volume in the diclofenac group and concluded that there had been increased bleeding in these patients.

*Respiratory depression*

Pain relief was hard to obtain despite large opioid doses in the women who had undergone immediate breast reconstruction and we experienced three incidents of respiratory depression among these women (respiratory rate < 6 breaths/minute) during the project. Two occurred shortly after arrival on the surgical ward due to post-operative care unit nurses' efforts to relieve their pain with increasing doses of opioids. The two women were not included in our study but our knowledge of these adverse events – together with poor relief of pain and large opioid consumption in the breast-reconstructed patients in our first study – raised the question of whether this specific type of surgery causes pain that is less opioid-responsive. In study III, similarly, one incident of hypoventilation occurred in the placebo group after 26 mg of self-administered morphine from the PCA device and 5 mg from a nurse within the first four post-operative hours. All three women were treated with naloxone and required continuous surveillance for several hours. Respiratory depression occurs in patients using PCA, most audits suggesting 0.1-0.8% of all patients without background infusion [98]. Another study examining the evidence from published data suggests 1.2% [22].

## Long-term persistent pain after breast cancer surgery – Study I

In our first study we contacted this study group with a questionnaire after 3-4 years to elicit the prevalence

of long-term pain (LTP), and 28/110 (25%) reported some degree of remaining pain. A majority of these patients (24/28) had also undergone lymph-node dissection, all mastectomy and eight breast reconstruction with submuscular expander prosthesis. We did not investigate their pain problem thoroughly but we know, by comparing the lymph dissections (ML) with the breast reconstructions (MR), that the axillary operations rated the greatest pain in the long-term perspective, while the reconstruction patients rated more pain and consumed more analgesics in the immediate postoperative period. Finally, 32% of the patients suffering long-term pain were recruited from the group who had undergone both immediate reconstruction and lymph dissection (MRL). These patients rated the highest pain and consumed most analgesics postoperatively, but they had also had extensive surgery. However, we do not know whether and how far the three variables acute pain, axillary dissection and/or breast reconstruction affected the development of these women's pain years after the operation.

Several types of long-term pain (LTP) syndrome after breast cancer surgery occur and are described in the literature: phantom breast pain, scar pain, chest wall pain and pain in the arm [160 83 173]. This persisting morbidity from breast surgery is common [82 129 167 170]. Unfortunately many women have suffered and still suffer from misdiagnosed and inadequately treated, long-lasting pain after different types of breast surgery [100 160].

Predisposing factors for post-treatment pain in the breast area and the ipsilateral arm may relate to type of surgery, nerve injury, radiotherapy, number of lymph nodes removed, post-surgery complications and/or age and acute postoperative pain intensity. Several authors have found breast conservative surgery more disposing to pain than radical modified mastectomy [21 166]. Increasing frequency of post-mastectomy pain syndrome at younger ages was found by several authors [128 155 96]. Tasmuth et al showed that acute postoperative pain intensity was the most disposing factor [166]. Other authors have similarly shown acute pain disposing for chronic pain [69 70]. However, the memory of previous acute pain can be influenced by the severity of the current persisting pain [41 44].

Regarding age, we found no significant differences between patients with or without LTP. In two subgroups (M and ML) the LTP patients had lower mean ages than those without LTP, but the difference was not statistically significant. An interesting finding shared by others was that women with LTP after breast cancer surgery do not usually use any pharmacological treatment for relief of their sometimes severe pain [20]. Enduring post-surgical pain for more than three years may have taught the women to cope using non-

pharmacological self-treatment methods. An attempt to address such ongoing pain through screening of all patients for post-mastectomy pain and offering pain-management strategies within six months after surgery is suggested [21].

However, many women feel that the quality of their life is affected by pain a long time after breast cancer surgery, and any attempt to rectify neglect of long-term pain in this patient group is desirable.

# CONCLUSIONS

The general conclusion of the thesis is that the drug combinations investigated resulted in reduced opioid consumption and improved pain relief in patients suffering moderate-to-severe postoperative pain.

Specifically:

- Intravenous opioid treatment administered with patient-controlled analgesia (**PCA**) technique was superior to conventional nurse-given intravenous injections in relieving pain after breast-cancer surgery, but the opioid consumption was higher.
- Rectal **diclofenac** compared to placebo in addition to opioids and paracetamol after immediate breast reconstruction and compared to opioids alone after caesarean section provided less pain and opioid consumption. However pain on movement after breast reconstruction was not significantly more efficiently treated with diclofenac than with placebo as an adjunct.
- Locally-instilled **levobupivacaine** compared to placebo in addition to opioids and paracetamol resulted in less pain after delayed breast reconstruction. However, 7/21 patients still rated 7 or more on the VAS during the first postoperative hour. This cannot be considered satisfactory. The morphine consumption was reduced but this was not statistically significant.
- Multimodal pain treatment did not result in any provable differences in **nausea and tiredness**. Post-operative **bleeding** was higher with diclofenac than with placebo treatment and more pronounced after extensive surgery. Two diclofenac-treated patients received blood transfusions but none was re-operated due to haematoma.
- The prevalence of **long-term persistent pain** after breast cancer surgery was 25%. There was no correlation between post-operative pain intensity and long-term prevalence or VAS scores. Most of the patients (24/28) reporting long-term pain had undergone axillary dissection.

# SUMMARY

Among women undergoing operations for breast cancer we found that reconstruction with tissue expander implant was associated with more intense pain and considerably higher opioid consumption than were other types of breast surgery. During the project period we experienced three serious hypoventilation events in patients with breast reconstruction. These were due to side-effects of high morphine consumption, and two occurred during the time of the first study. These events raised the question of poor-opioid-responsive pain and led us to further investigate combination analgesic strategies aiming at reduced opioid need and improving pain relief:

> After breast reconstruction with expander implant. This is because opioid PCA treatment (as a single-mode method) obviously increased the risk of opioid consumption reaching levels high enough to cause serious side- effects such as respiratory depression.
>
> After caesarean section. This is because it is important and beneficial to mother and child and their interaction to limit the need for opioids and also because uterine contraction pain is little sensitive to opioids.

We conclude that the patient categories we have studied should preferably receive pain treatment in a multimodal way. Opioid PCA as a single-mode method can even be risky in patients with pain with low opioid sensitivity. Although the analgesic combinations we studied were more efficacious than opioids alone, they were not ideal; the severe pain still experienced in the very first postoperative hours after breast reconstruction must be managed. Also pain during movement should be more adequately controlled. For this further research is needed.

With the exception of the questionnaire described above, persistent pain after breast cancer surgery was not studied in the present work. Our prospective and detailed investigation of post-operative pain after breast reconstruction could usefully be followed up over a longer term, if our respondents could be persuaded to contribute once more.

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Namn:.....

**Fick Du i samband med Din operation någon av följande tilläggsbehandlingar?**

☐ Hormonbehandling ☐ Kemoterapi (Cytostatikabehandling) ☐ Strålbehandling

## FRÅGOR OM SMÄRTA

**1. Har Du haft ont från det opererade bröstet eller från samma sidas arm under den senaste månaden?**

☐ NEJ ☐ JA

Om Du svarat JA på ovanstående fråga, var snäll och besvara följande frågor.

**2. Har du ont just nu?**

☐ NEJ ☐ JA

**3. Hur stark är smärtan när den är som sämst och som lindrigast? Markera med två kryss på linjen.**

_____

**ingen smärta** **värsta tänkbara smärta**

**4. Känns smärtorna djupa eller ytliga?**

☐ djupa ☐ ytliga ☐ både djupa och ytliga

☐ huden är överkänslig för beröring

**5. Använder Du smärtstillande mediciner mot denna smärta?**

☐ Nej ☐ Ja, regelbundet ☐ Ja, vid behov

Vilka? _____

Vilken effekt upplever Du av dessa? ☐ Ingen ☐ Måttlig ☐ God

**6. Finna det något annat som lindrar Din smärta?**

☐ NEJ ☐ JA

Om ja, i så fall vad? _____

**7. Finns det något som förvärrar Din smärta?**

☐ NEJ ☐ JA

Om ja, i så fall vad? _____

**8. Inskränker smärtan Dig i Dina dagliga aktiviteter?**

☐ Nej, inte alls ☐ Ja, delvis ☐ Ja, mycket