Department of Anaesthesia and Intensive Care Medicine
and Department of Clinical Pharmacology,
University of Helsinki,
Finland

PAIN AFTER THORACIC SURGERY

by

Kristiina Perttunen

ACADEMIC DISSERTATION

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Supervised by:

Docent Eija Kalso, MD, D. Med. Sci.

Pain Clinic
Department of Anaesthesia and Intensive Care
University of Helsinki
Helsinki, Finland

Reviewed by:

Docent Riku Aantaa, MD

Department of Anaesthesia
Turku University Hospital
Turku, Finland

Professor Seppo Alahuhta, MD

Department of Anaesthesia
Oulu University Hospital
Oulu, Finland

Opponent:

Docent Heikki Hendolin, MD
Department of Anaesthesia
Kuopio University Hospital
Kuopio, Finland

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To all patients suffering from postoperative pain

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1 ABBREVIATIONS

ADH	antidiuretic hormone
ANOVA	analysis of variance
anti-AChR-ab	acetylcholine receptor antibodies
ASA	American Society of Anesthesiologists
BP	blood pressure
cAMP	cyclic adenosine monophosphate
COX	cyclooxygenase
EMG	electromyography
$ETCO_2$	end tidal carbon dioxide
FEV_1	forced expiratory volume (in 1 sec)
FiO_2	fraction of inspired oxygen
FVC	forced vital capacity
HLA	human leukocyte antigen
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
IASP	International Association for the Study of Pain
i.m.	intramuscular(ly)
i.v.	intravenous(ly)
i.t.	intrathecal(ly)
IVY	bleeding time using the method published by Ivy (1941)
K/R+K	coagulation time
MA	maximum amplitude
Mo	morphine
NaCl	sodium chloride
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
$PaCO_2$	carbon dioxide tension in arterial blood
PACU	postoperative anaesthesia care unit
PaO_2	oxygen tension in arterial blood
PCA	patient controlled analgesia
PCEA	patient controlled epidural analgesia
PTPS	postthoracotomy pain syndrome
R	reaction time
RR	respiratory rate
s.c.	subcutaneous
SEM	standard error of mean
SpO_2	pulse oximetry
TEG	thromboelastography
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale
VAS%	percentage of the maximum value on a visual analogue scale
VAS_{pi}	visual analogue scale pain intensity
VATS	video-assisted thoracic surgery
VRS	verbal rating scale

2 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:

I Kalso E, Perttunen K, Kaasinen S. Pain after thoracic surgery. Acta Anaesthesiol Scand 36: 96–100, 1992

II Perttunen K, Kalso E, Heinonen J, Salo J. I.v. diclofenac in post-thoracotomy pain. Br J Anaesth 68: 474–480, 1992

III Perttunen K, Nilsson E, Heinonen J, Hirvisalo E-L, Salo JA, Kalso E. Epidural, paravertebral and intercostal nerve blocks in post-thoracotomy pain. Br J Anaesth 75: 541–547, 1995

IV Perttunen K, Nilsson E, Kalso E. Intravenous diclofenac and ketorolac for pain after thoracoscopic surgery. Br J Anaesth 82; 221–227, 1999

V Nilsson E, Perttunen K, Kalso E. Intrathecal morphine for post-sternotomy pain in patients with myasthenia gravis: effects on respiratory function. Acta Anaesthesiol Scand 47: 549–556, 1997

VI Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiol Scand 43: 563–567, 1999

3 ABSTRACT

Pain treatment after thoracic operations is particularly important because the postoperative recovery of patients undergoing thoracic surgery is dependent on the maintenance of respiratory function. Respiratory depression is one of the disadvantages of opioids commonly used for postoperative pain treatment. On the other hand, there are several regional analgesic methods, which can be used for pain treatment after thoracic surgery without the adverse events associated with opioids. These techniques include intercostal, intrapleural, intraspinal and paravertebral blockade. Nonsteroidal anti-inflammatory drugs (NSAIDs) have become popular in combination with opioids for treatment of postoperative pain, although no reliable data exist on the intravenous dosage of NSAIDs.

The objective of the present series of studies was to compare the efficacy and adverse events of intravenous morphine, NSAIDs and three different local analgesic methods in pain relief after two types of thoracic surgery, and to compare the efficacy and adverse events of intravenous and i.t. morphine in pain relief after transsternal thymectomy in myasthenia gravis patients, who are especially in danger of postoperative respiratory depression. This series of studies was also intended to investigate the incidence, duration and severity of persistent postthoracotomy pain, and to assess the associated risk factors.

Altogether 442 patients were included in these six different studies. Study I with 207 thoracotomy patients was a retrospective study whereas study VI with 110 thoracotomy patients was a prospective follow-up study. Studies II and IV were randomised, placebo-controlled studies with 30 patients in each undergoing thoracic surgery and studies III and V were open, randomised studies with altogether 65 patients undergoing thoracic surgery.

All patients in the consecutive studies II – V were allowed to take supplementary doses of morphine intravenously from a patient-controlled analgesia (PCA) device during the first two postoperative days. Visual analogue scale (VAS) (studies II – V), four-point verbal rating scale (VRS) (studies II – IV), five-point verbal rating scale (study VI) and the McGill pain questionnaire (study VI) were used for pain measurement. Arterial blood gas analysis was performed in studies II – V up to the second postoperative day. Special attention was paid to urinary output in studies II and IV. Haematological effects were measured in studies II and IV using the IVY bleeding time, the platelet adhesion test (Adeplat S®) and thromboelastography. Drug concentrations were measured in studies III – V. In studies II – V the patients were evaluated for adverse events and were asked to rate their performance status. Patients in the questionnaire studies (studies I and VI) were interviewed using standardised questions.

The incidence of chronic postthoracotomy pain was 80% at 3 months, 75% at 6 months and 61% one year after surgery (study VI). The incidence of severe pain was 3 – 5%. Chronic postthoracotomy pain interfered with normal daily life in more than half of the patients. In study I cumulative opioid consumption during the first 24 hours was 57 – 61% lower than in thoracotomy studies II – III whereas in study VI cumulative opioid consumption was only 9 – 18% lower. On the basis of the visual analogue scale pain intensity at rest (VAS_{pi}) control patients experienced more pain after thoracotomy compared with thoracoscopy (48% vs. 34% of the maximum value). The mean cumulative morphine consumption in the control patients in thoracotomy studies II – III after the first 24 hours was 72.5 – 80.4 mg whereas in the thoracoscopy study (IV) it was 66.6 mg and in the sternotomy

study (V) it was 50.4 mg. In study II, the consumption of morphine was 60% lower than in the control group on the first postoperative day and 76% lower on the second postoperative day. In study IV, the mean consumption of morphine in the control group was 57 mg; both diclofenac and ketorolac were equally effective in reducing total morphine consumption (61% and 52%, respectively). In study III, all three local anaesthetic methods, intrapleural, epidural and paravertebral, provided equally effective pain relief after thoracic surgery. In study III moderate to severe respiratory depression was detected in 14 of 45 patients more than 2 hours after surgery. In thymectomy patients (study V), FVC recovered to 60% of baseline and FEV_1 to 57% in the i.t. morphine group compared with 32% and 37% in the PCA morphine group.

It is concluded that postthoracotomy pain is usually severe and may require high doses of opioids. Intravenously administered NSAIDs improved analgesia and significantly reduced morphine consumption. NSAIDs were safe with regard to both haemostasis and renal function. None of the three local anaesthetic techniques with comparable risk-benefit ratios used in the studies, i.e. intercostal, epidural and paravertebral blockade, produced good pain relief after thoracotomy. The required PCA-doses of morphine were high and respiratory depression occurred in one third of the patients. In myasthenia gravis patients i.t. morphine provided effective poststernotomy pain relief and significantly improved ventilatory function when compared with PCA morphine. The high incidence of postpuncture headache was a serious disadvantage. In myasthenia gravis patients careful postoperative monitoring is required because of the relatively compromised muscle strength in these patients and the attendant possibility of respiratory depression due to pain therapy. Chronic postthoracotomy pain is a serious problem following surgery for benign and malignant disease alike.

4 INTRODUCTION

It is a well-known fact that many patients experience moderate to severe pain after surgery due to inadequate pain treatment and every effort should be made to overcome this phenomenon. One of the most severe types of postoperative pain has been reported after thoracic surgery. Some patients develop chronic postthoracotomy pain that may last for months or years. In addition, severe postoperative pain contributes to postoperative pulmonary dysfunction. The choice of perioperative analgesic technique may play an important role here. The sources of pain are multiple, i.e. the site of the surgical incision, damage to ribs and intercostal nerves, inflammation of chest wall structures, incision or crushing of pulmonary parenchyma or pleura, and the placement of thoracotomy drainage tubes. Systemic opioids have been used traditionally for the treatment of postthoracotomy pain, but in recent years new methods and techniques, i.e. nonsteroidal anti-inflammatory drugs, epidural or intrathecal opioids and different regional analgesic techniques, have become more popular. However, some of these new delivery systems and techniques are potentially hazardous.

Numerous studies are available concerning pain treatment after thoracic surgery, but there still is no effective pain treatment, which carries a minimum of risk, is cost effective and is easy to put in to practice. The present series of studies was carried out to assess the effectiveness of intravenous and intrathecal morphine, nonsteroidal anti-inflammatory drugs and three different regional analgesic techniques after three types of thoracic surgery. Two of the studies investigated the incidence, duration, severity and risk factors of persistent postthoracotomy pain.

5 REVIEW OF LITERATURE

5.1 Pain after thoracic surgery

5.1.1 Definition of pain

Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (International Association for the Study of Pain, Subcommittee of Taxonomy 1986b). Acute pain is a physiologic reaction to acute trauma or tissue damage. Pain is chronic if it recurs or persists (e.g. along a thoracotomy scar) at least two months following the surgical procedure (International Association for the Study of Pain, Subcommittee of Taxonomy 1986a). Pain is always subjective and unpleasant and therefore also an emotional experience (International Association for the Study of Pain, Subcommittee of Taxonomy 1986b).

5.1.2 Neurophysiology of pain

5.1.2.1 Peripheral tissues

Peripheral pain receptors (nociceptors) can be identified in all tissues. Pain is usually initiated by excitation of nociceptors or afferent nerve fibres. These fibres belong to the A-δ and C classes. The small-diameter myelinated A-δ fibres are associated with sharp, well-localised pain and unmyelinated C fibres with dull, burning diffusely localised pain. The C-fibre conduction rate is much slower than that of the A-δ fibres. C-fibre activity predominates in continuing pain. The C fibres also include efferent sympathetic fibres, which probably increase the sensitivity of peripheral nociceptors to pain. These primary afferent nerve fibres, i.e. A-δ and C fibres, project to the dorsal horn of the spinal cord. They represent the first site in the pain pathway where pain conduction can be modulated (Phillips and Cousins 1986).

Responsiveness of peripheral pain receptors can be increased by factors which include physical stimuli, the chemical environment, endogenous algesic substances as prostaglandins, serotonin and bradykinin, changes in the microcirculatory blood supply, and increased efferent sympathetic activity (Phillips and Cousins 1986).

Nociceptive visceral afferents are sympathetic fibres, which pass via cervicothoracic sympathetic ganglia from thoracic viscera to the dorsal horn neurons in the spinal cord. Here visceral afferents converge on the same dorsal horn neurons as somatic nociceptive afferents. Peripheral visceral afferents branch considerably, causing much overlap in the territory of individual dorsal roots. Visceral afferents converge on the dorsal horn over a large number of segments. Therefore, visceral pain is poorly localised and vague, may be cramping and aching and may be referred to another area (Phillips and Cousins 1986).

5.1.2.2 Spinal cord

Cell bodies of primary afferent fibres are contained in dorsal root ganglia and trigeminal sensory ganglia. Primary afferent transmission usually begins in the peripheral processes and travels centrally past dorsal root ganglion cells to the dorsal roots. Large fibres from the dorsal root enter the dorsal columns, but collaterals also go to the dorsal horn (Phillips and Cousins 1986). Fine fibres enter a longitudinal tract before entering the dorsal horn areas. In the ventral roots 15 to 30 percent of axons are sensory (Coggeshall et al. 1975). The synapse between the small diameter afferent fibres and the dorsal horn neuron of the spinal cord represents the second site in the pain pathway where pain conduction can be modulated.

Certain cells in the dorsal horn of the spinal cord respond preferentially or exclusively to nociceptive input. Substance P, an undecapeptide, is present in the terminals

of nociceptive neurons in the dorsal horn. Peripherally stimulated A-δ fibres induce the release of substance P in the spinal cord (Cousins and Bridenbaugh 1998). Administering opioids before stimulating nerve fibres decreases substance P release, which would appear to indicate a presynaptic effect of opioids on various nociceptive fibres (Jessel and Iversen 1977). Other peptides that may play a role in primary afferent transmission include neurotensin, vasoactive intestinal peptide, and cholecystokinin. Inhibition of transmission by descending pathways probably involves noradrenergic, serotonergic, enkephalinergic, and gamma-aminobutyric acid (GABA) systems (Yaksh and Chaplan 1997, Cousins and Bridenbaugh 1998).

5.1.2.3 Brain

Nociceptive information is transmitted to different regions of the brain by ascending tracts which include the spinothalamic tract, the spinomesencephalic tract, the spinoreticular system and diffuse polysynaptic connections which relay nociceptive information within the cord. Descending tracts arise from the brain stem raphe nucleus and reticular formation. Descending inhibition exercises continuous control of afferent input to the dorsal horn. Both opioid and nonopioid inhibitory systems may respond to different types of pain or stress. The brain stem reticular area transmits all ascending and descending stimuli (Phillips and Cousins 1986).

Thus, very complex neural connections involving diverse areas of the nervous system play a part in pain. Pain may be modulated at the spinal cord level, in the periaqueductal grey matter and brain stem raphe nuclei prior to reaching relays and gating mechanisms in the thalamus on the way to the cerebral cortex.

5.1.3 Pain after thoracic surgery

Pain after thoracic surgery can be both nociceptive and visceral. The pain syndromes that develop after thoracic surgery take many forms. Their classification is based on the origin of pain in specific visceral, musculoskeletal, neural, and dermal tissues (Raj and Brannon 1993).

Nociceptive pain after thoracic surgery is due to tissue damage and is mediated mostly via intercostal nerves from the structures of the chest wall and most of the pleura, via the phrenic nerve from the diaphragmatic pleura and via the vagal nerve from the lung and mediastinum including the mediastinal pleura (Conacher 1990, Cervero and Laird 1999). Visceral pain after thoracic surgery is due to pleural irritation and is mediated from the pleura through sympathetic nerves to the central nervous system (Conacher 1990, Cervero and Laird 1999). Thoracic musculoskeletal pain is related to surgical trauma and postsurgical changes (Raj and Brannon 1993, Wallace and Wallace 1997). The most common persistent pain following thoracic surgery is related to myofascial structures, i.e. muscle, bone, tendon, and ligament (Raj and Brannon 1993). Thoracic fascitis following thoracotomy is also common but the most common source of myofascial pain is the muscle (Raj and Brannon 1993, Wallace and Wallace 1997). Patients can also experience severe pain caused by chest tubes after thoracic surgery if the tubes compress the intercostal nerves. Retractors used in the surgical procedure can cause rib fractures, which can be very painful and limit respiratory function. The intercostal nerves may be damaged if sutures or wires are passed around the ribs close to the neurovascular bundle. Neural pain caused by intercostal neuralgia following thoracotomy is particularly common. This kind of pain is burning, lancinating, and aggravated by stretching the affected nerve and also gets worse at night (Raj and Brannon 1993). Hyperalge-

sia is often associated with the wound itself. Secondary hyperalgesia possibly results from central sensitisation. Also, local release of inflammatory chemical mediators occurs with tissue damage. These mediators, which include hydrogen ions, serotonin (5HT), histamine, bradykinin, substance P, prostaglandins, and leukotrienes, have indirect effects on the nociceptor (Mattison 1990, Dray et al. 1994). Management of neuropathic pain requires the tools to identify the mechanism responsible for the pain in a particular individual, and then the capacity to reverse the mechanisms (Woolf and Mannion 1999).

5.1.4 Degree and duration of pain after thoracic surgery

The degree of pain after thoracic surgery is generally rated as "severe". Pain after thoracotomy has been described as one of the most severe modes of postoperative pain (Loan and Morrison 1967, Benedetti et al. 1984). In a survey performed in the 1960's in England (Loan and Morrison 1967) more than 70% of patients required analgesics during the immediate postoperative period after thoracotomy compared with approximately 60% after upper abdominal operations and only about 50% after lower abdominal operations. According to these authors (Loan and Morrison 1967, Benedetti et al. 1984) special attention should be given to the treatment of postoperative pain after thoracic surgery because of the severity of the pain. Salzer with colleagues (Salzer et al. 1997) presented controversial results concerning the pain after thoracic surgery. Comparison of postoperative pain during the first days after posterolateral thoracotomy and median laparotomy showed that the patients undergoing median laparotomy used significantly more piritramide during the first 4 postoperative days than the patients udnergoing posterolateral thoracotomy. The VAS scores were also lower in the thoracotomy group (Salzer et al. 1997).

Published and unpublished data concerning the incidence and duration of pain compiled by Benedetti with colleagues indicate that postoperative pain occurs more often and is more severe following intrathoracic (i.e. thoracotomy or sternotomy) surgery than following orthopaedic or abdominal surgery. The intensity of steady wound pain after thoracotomy was severe in 45 – 65% of the patients and moderate in 25 – 35% of the patients. After sternotomy steady wound pain was severe in 60 – 70% of the patients and moderate in 25 – 35% of the patients. After intrathoracic operations, movements that place tension on the incision, such as deep breathing, coughing, or extensive body movements, increase the intensity of pain. In this survey the average duration of severe pain was 3 days (range: 2 – 6 days) after thoracotomy and 4 days (range 2 – 7 days) after sternotomy (Benedetti et al. 1984).

Less invasive methods of thoracic surgery than open thoracotomy have been developed during the last 15 years. Patients undergoing video-assisted thoracic surgery (VATS), i.e. thoracoscopy, experienced significantly less postoperative pain compared to patients undergoing lateral thoracotomy. Patients undergoing VATS required less patient-controlled intravenous morphine versus patients undergoing lateral thoracotomy. The postoperative hospital stay was also shorter after VATS than that required for patients undergoing lateral thoracotomy (Landreneau et al. 1993). Patients undergoing axillary thoracotomy have been shown to have significantly higher pain scores using VAS than patients undergoing VATS. Consumption of subcutaneous piritramide, a synthetic opioid derivative, as an indirect subjective pain indicator was significantly higher at all time points in the patients who underwent thoracotomy (Tschernko et al. 1996).

There are several different incisions used by surgeons for access to the thorax. Lateral thoracotomy is usually performed at the level of the fourth, fifth, sixth or seventh rib spaces and the skin incision may extend from the second thoracic dermatome pos-

teriorly to the eighth dermatome close to the sternum (Conacher 1987). Anterolateral muscle-sparing thoracotomy has been reported to be postoperatively less painful than the posterolateral approach (Hazelrigg et al. 1991). Posterolateral thoracotomy is the most painful route for surgical access (Baeza and Foster 1976). Median sternotomy and anterolateral thoracotomy are notably less painful. Unfortunately, access to some intrathoracic structures via median sternotomy is often limited (Baeza and Foster 1976, de la Rocha and Chambers 1984). Pain following thoracotomy usually resolves within two months after surgery. Pain after thoracic surgery is considered chronic if it persists for more than two months. Pain that persists beyond this time or recurs may have a burning, dysesthetic component (International Association for the Study of Pain, Subcommittee of Taxonomy 1986a).

5.2 Pain management after thoracic surgery

5.2.1 Systemic analgesia

Systemic analgesia may be divided into systemic opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol and ketamine. Opioids, NSAIDs, and ketamine can be delivered using intravenous, intramuscular or subcutaneous routes. Patient-controlled analgesia devices (PCA) can be useful when administering intravenous opioids. Combinations of NSAIDs and opioids or opioids and regional analgesia are also common.

5.2.1.1 NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, an enzyme which controls the synthesis of prostaglandins, prostacyclins, and thromboxanes. All three may be involved in pain (Juan 1978). Blockade of pain by NSAIDs is thus a peripheral and central action compared with the predominantly central action of opioids.

NSAIDs including diclofenac, indomethacin, ketorolac, lysine acetyl salicylate, piroxicam, and tenoxicam have been used as analgesics to reduce pain after thoracic surgery (Jones et al. 1985, Pavy et al. 1990, Bigler et al. 1992, Merry et al. 1992, Rhodes et al. 1992, Kavanagh et al. 1994b, Power et al. 1994, Singh et al. 1997). Potential adverse effects include gastrointestinal bleeding, acute reversible renal dysfunction and systemic bleeding associated with platelet dysfunction irrespective of the route of administration (Camu et al. 1992, Kenny 1992, Johnson et al. 1994, Bugge 1995, Ellenhorn et al. 1997, Lee et al. 1999). NSAIDs can be given intravenously, intramuscularly, orally or rectally (Tigerstedt et al. 1987, Pavy et al. 1990, Kavanagh et al. 1994a, Carretta et al. 1996, Hynninen et al. 2000). There are only a few NSAIDs which can be delivered parenterally. In Finland these are diclofenac, ketoprofen, indomethacin, meloxicam and ketorolac tromethamine (Laitinen et al. 1992, Kostamovaara et al. 1998).

Intramuscular diclofenac in a dose of 75 mg every 12 hours for three days as an adjunct to papaveretum for pain after lateral thoracotomy resulted in lower consumption of papaveretum and in lower visual analogue scale (VAS) pain scores throughout the study period compared with the patients given only papaveretum for analgesia (Rhodes et al. 1992).

Rectally administered indomethacin reduced postoperative VAS pain scores by 60% while the reduction in opioid consumption was approximately 30%. The daily dose of indomethacin was 200 mg and the cumulative papaveretum dose in the indomethacin group was approximately 70 mg during the first 48 hours. Unfortunately, PCA was not used for supplementary analgesia and therefore the need for supplementary analgesics may have been misinterpreted (Pavy et al. 1990).

Ketorolac has been shown to reduce the need for patient-controlled epidural analgesia (PCEA) with hydromorphone after thoracotomy compared with epidural bupivacaine

while the resting pain scores were comparable in both treatment groups (Singh et al. 1997). I.m. ketorolac as a component of balanced analgesia failed to improve analgesia after thoracotomy. However, it was difficult to show any differences in PCA morphine use or pain scores in this study because of the large number of patients who withdrew from the control group (Power et al. 1994).

Continuous infusion of i.v. lysine acetyl salicylate (7.2 g in 24 h) compared with infusion of i.v. morphine (40 mg in 24 h) has been shown to be equally effective in treatment of postthoracotomy pain. The VAS pain scores and PCA papaveretum use were similar in both groups (Jones et al. 1985). Intravenous tenoxicam (20 mg) reduced the consumption of i.v. papaveretum delivered with a PCA device for postoperative pain treatment after lateral thoracotomy. The tenoxicam group used less rescue papaveretum during the first 12 hours than the placebo group. There were no significant differences between the groups in VAS pain scores or adverse events (Merry et al. 1992).

Acute renal failure is one of the potentially most serious adverse events associated with the use of NSAIDs during and after surgery especially in patients with pre-existing renal disease or hypovolemia and in patients taking loop diuretics.

Renal prostaglandins regulate the water balance and the excretion of sodium and potassium. They contribute more to the maintenance of renal haemodynamics under adverse conditions than under normal circumstances (Clive and Stoff 1984). Therefore, inhibition of prostaglandin synthesis may have profound consequences for renal blood flow and glomerular filtration rate when it is superimposed on a preceding haemodynamic insult e.g. hypovolemia, hypotension (Henrich et al. 1978), salt depletion (Blasingham and Nasjletti 1980) or heart failure (Oliver et al. 1981). Anaesthesia and surgery can decrease renal blood flow as a result of hypovolemia and hypotension. Moreover, the stress response triggered by surgery increases secretion of antidiuretic hormone (ADH) which normally stimulates the production of medullary prostaglandins. These medullary prostaglandins can moderate the tubular effects of ADH by inhibiting the generation of cAMP (Christensen 1978). NSAIDs have also been shown to enhance the effects of exogenous vasopressin (Clive and Stoff 1984).

Increased knowledge about the mechanism of prostaglandin synthesis and the role of COX isoenzymes has led to the development of COX-2 selective nonsteroidal anti-inflammatory drugs (Jackson and Hawkey 2000). These selective NSAIDs might be beneficial compared to ordinary NSAIDs because they may minimise COX-1-dependent adverse events, i.e. gastroduodenal toxicity, while offering analgesia, a reduction in opioid requirements, and the potential to reduce the incidence of chronic pain after surgery and, possibly, also nausea and vomiting (McCrory and Lindahl 2002). Celecoxib showed better tolerability and a lower frequency of gastrointestinal adverse events with similar analgesic efficacy compared to diclofenac (Emery et al. 1999). Tang and co-workers demonstrated a significant opioid sparing effect with parecoxib, an intravenous COX-2 inhibitor, in 55 patients undergoing lower abdominal surgery (Tang et al. 2002). On the other hand, these new COX-2 inhibitors are associated with an increased rate of cardiovascular events, i.e. myocardial infarctation, unstable angina, and ischaemic stroke (Mukherjee et al. 2001).

5.2.1.2 Opioids

Postoperative analgesia after thoracic surgery traditionally consists of intramuscular, intravenous or subcutaneous administration of opioids (Gravlee and Rauck 1993). Opioids including morphine, fentanyl, pethidine (= meperidine), buprenorphine, piritramide, papaveretum and tramadol have been used parenterally for pain relief after thoracic surgery (Shulman et al. 1984, Sandler et al. 1992, Deneuville et al. 1993,

Kavanagh et al. 1994a, Slinger et al. 1995, James et al. 1996, Tschernko et al. 1996, Salzer et al. 1997). Tramadol is an analgesic with mixed μ-opioid and nonopioid activity. The nonopioid component is mediated through increased α_2-agonist and serotonergic activity (Scott and Perry 2000). Intravenous opioids can be delivered as bolus doses or as a continuous infusion. Postthoracotomy studies exist on the use of intramuscular opioids alone, subcutaneous opioids, nurse-controlled intravenous opioids and intravenous PCA (Lehmann 1990, Kavanagh et al. 1994b, Salzer et al. 1997). The main advantage of i.v. PCA is, that it takes into sufficient consideration the different subjective pain sensitivities of each patient (Salzer et al. 1997). The narrow therapeutic window is the major problem when using opioids. Even moderate doses of opioids can result in adverse effects such as nausea or vomiting, somnolence and respiratory depression (Jordan et al. 1979). Pulmonary dysfunction is a major problem especially after thoracotomy.

Multimodal analgesia with morphine 0.15 mg/kg i.m., perphenazine 0.03 mg/kg i.m. and a rectal suppository of indomethacin 100 mg one hour before lateral thoracotomy resulted in slightly lower consumption of PCA morphine in the first 6 h after surgery compared to a control group receiving midazolam 0.05 mg/kg i.m. preoperatively. However, cumulative morphine consumption at 72 h after surgery was greater in the treatment group (185 mg) compared with the control group (150 mg) (Kavanagh et al. 1994b).

Fixed-schedule i.m. buprenorphine (0.3 mg buprenorphine i.m. given every 8 hours for the first 5 days) was equally effective in pain relief after thoracotomy compared with continuous intercostal analgesia with bupivacaine. Unfortunately, supplementary analgesics were only given on request and PCA was not used in this study (Deneuville et al. 1993).

Subcutaneous piritramide demand was significantly higher in the patients undergoing thoracotomy compared with patients undergoing VATS. The injections were given s.c. as a bolus, using no more than 7.5 mg piritramide within 45 min (Tschernko et al. 1996).

A single i.v. bolus dose of 150 mg tramadol provided analgesia which was as effective as continuous epidural morphine for a period of 24 hours after thoracotomy. All patients were provided with an i.v. PCA device that delivered 1.5 mg bolus doses of morphine with a lockout time of 8 min (James et al. 1996). Continuous i.v. tramadol infusion was shown to be equally effective as epidural morphine infusion in 30 patients undergoing posterolateral thoracotomy. All patients received additional i.v. morphine boluses in 1.5 mg increments with a PCA device (Bloch et al. 2002).

5.2.1.3 Ketamine

Ketamine is a non-competitive antagonist which blocks the ion channel coupled to the *N*-methyl-D-aspartate (NMDA) receptor and hence central hyperexcitability of dorsal horn neurons. The action of the excitatory amino acids has been extensively shown to be mediated via the NMDA receptor and non-NMDA receptors. The NMDA receptor has been implicated in a number of long-term events in the central nervous system (CNS). In vitro studies have shown that both A-δ and C-fibre activation increase aspartate and glutamate outflow at the level of the spinal cord. Activity in the former, low threshold fibres appears to normally activate only the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. The activities needed for NMDA-receptor activation are much more complex and only appear to be achieved by repeated C-fibre activity (Dickenson 1995).

The effect of a ketamine 0.5 mg/kg bolus followed by a 20-min infusion of 9 μg/kg/min ketamine on the response to repeated nociceptive stimuli (central temporal summation) was investigated in 12 human volunteers in an experimental crossover study. The reaction time after ketamine

was significantly ($P < 0.01$) prolonged compared to placebo. Significant increases in pain detection and pain tolerance thresholds were found compared with placebo ($P < 0.001$). The psychophysical responses, the summation reflex thresholds, and the VAS responses to repeated stimuli were changed significantly by ketamine compared with placebo ($P < 0.001 – P < 0.01$). The investigators concluded that ketamine inhibits central temporal summation in humans and has a marked hypoalgesic effect on high intensity nociceptive electrical and mechanical stimuli (Arendt-Nielsen et al. 1995).

Low-dose i.m. ketamine and i.m. pethidine after thoracic surgery have been shown to be equally efficacious but there was less respiratory depression in the ketamine group. The patients were randomised to receive an i.m. injection of either pethidine 1 mg/kg or ketamine 1 mg/kg whenever needed. There were no significant differences in the pain scores between the two groups during the study, but the pain scores tended to be lower in the pethidine group during the first 2 hours and in the ketamine group after 3 hours (Dich-Nielsen et al. 1992).

Ketamine has also been used as a part of multimodal patient-controlled epidural analgesia. Ketamine added to patient-controlled epidural analgesia (PCEA) resulted in significantly lower mean VAS scores during coughing or at rest for the first 3 postoperative days in patients undergoing major surgery. The study included 46 thoracotomy patients, of whom 26 received a regimen of morphine 0.02 mg/ml, 0.08% bupivacaine and adrenaline 4 µg/ml with addition of ketamine 0.4 mg/ml while 20 received the same treatment without ketamine. The PCEA infusion rate and bolus volume was titrated according to the analgesic effect. The cumulative mean multimodal regimen requirements of the control group on days 1 and 2 (96.6 ml and 189.1 ml, respectively) were significantly higher than those of the ketamine group (74.0 ml and 155.4 ml, respectively) (Chia et al. 1998).

These observations and the laboratory data concerning the role of *N*-methyl-D-aspartate (NMDA) receptor activation in postinjury central sensitisation and hyperalgesia suggest that systemic ketamine, a noncompetitive NMDA-antagonist, may be an important tool in the treatment of postthoracotomy pain (Woolf and Thompson 1991, Chia et al. 1998, Chow et al. 1998).

5.2.2 Regional analgesia

There are several regional analgesic methods that can be used for pain management after thoracic surgery. These include intercostal, paravertebral, interpleural, epidural, and spinal blockade. Techniques that have been described for postthoracotomy analgesia include thoracic local anaesthetics, epidural opioids (including opioid agonist-antagonists), thoracic epidural opioids combined with local anaesthetics, thoracic epidural adrenergic agonists, and i.t. opioids.

5.2.2.1 Intercostal blockade

Intercostal blockade has been widely used for analgesia after thoracic surgery (Delilkan et al. 1973, Galway et al. 1975, Kaplan et al. 1975, Toledo-Pereyra and DeMeester 1979, Asantila et al. 1986, Chan et al. 1991, Swann et al. 1991, Deneuville et al. 1993, Dryden et al. 1993). The intercostal nerves are the primary rami of spinal nerves T1 through T11. Somatic innervation of the area from the nipples to below the umbilicus is provided by segmental spinal nerves from T4–T11. The intercostal nerve has four significant branches. These include rami communicantes, which pass anteriorly to and from the sympathetic ganglion and chain, the posterior cutaneous branch supplying the skin and muscles in the paravertebral region, the lateral cutaneous branch located in the midaxillary line, and the anterior cutaneous branch. The intercostal nerves lie between the pleura and the fascia of the internal intercostal muscle from the medial to the posterior angles of the

ribs. In the paravertebral region, there is only fatty connective tissue between nerve and pleura (Kopacz and Thompson 1998).

Local anaesthetics for intercostal blockade can be administered as a single bolus directly before chest closure (Delilkan et al. 1973, Galway et al. 1975, Kaplan et al. 1975, Toledo-Pereyra and DeMeester 1979, de la Rocha and Chambers 1984), as a single percutaneous injection (Swann et al. 1991), as multiple percutaneous injections (Asantila et al. 1986) or via an indwelling intercostal catheter (Chan et al. 1991, Deneuville et al. 1993, Dryden et al. 1993). The site of injection relative to the angle of the ribs and the attachment of the posterior intercostal membrane to the internal intercostal muscle has been shown to be important for the spread of local anaesthetic solutions (Kopacz and Thompson 1998). Injections through intercostal catheters directed medially spread to 3 to 5 intercostal spaces because the tips of the catheters end up 2 to 3 cm medial of the medial border of the intercostalis intimus muscle, where the solution can freely spread cephalad and caudad in the extrapleural space where the parietal pleura is less adherent to the ribs. Because of the eventual position of these catheter tips, they are probably more appropriately called 'continuous paravertebral catheters' than 'continuous extrapleural intercostal catheters' (Kopacz and Thompson 1998). The main disadvantage of the intercostal technique is the high level of systemic absorption of local anaesthetics (Chan et al. 1991).

Bupivacaine 0.5% 20 ml with adrenaline 5 µg/ml or normal saline administered by indwelling intercostal catheter every 6 h for 24 h after thoracotomy resulted in lower VAS pain scores after each injection. Opioid consumption was lower over 24 h in the bupivacaine group compared to the saline group (16.6 mg versus 35.8 mg). Repeated intercostal bupivacaine administration (a total of 400 mg in 24 hours) led to systemic accumulation with a peak bupivacaine concentration of 1.2 µg/ml, which is below the toxic range of 4 µg/ml (Chan et al. 1991). Continuous intercostal bupivacaine for pain relief after thoracotomy resulted in lower requirements of i.v. PCA morphine compared with placebo. Patients also recorded lower VAS pain scores while receiving bupivacaine. This study was designed as a crossover trial with patients receiving either bupivacaine for the first 24 hours and saline for the second or saline for the first 24 hours followed by bupivacaine (Dryden et al. 1993).

5.2.2.2 Paravertebral blockade

Paravertebral blockade is a unilateral block suitable for pain treatment after lateral thoracotomy (Sabanathan et al. 1988, Matthews and Govenden 1989, Sabanathan et al. 1990, Richardson et al. 1994, Richardson et al. 1999). The thoracic paravertebral space is continuous with the subpleural space at the tip of the transverse process. Its boundaries include the transverse process, vertebral body and intervertebral foramen, costotransverse ligament and pleura (Kopacz and Thompson 1998, Karmakar and Chung 2000). The thoracic paravertebral space is a potential space similar to the epidural space, filled with fat and containing both the intercostal nerves and rami communicantes, and its volume is much larger than that of the subcostal space. A thoracic paravertebral block will result in a regional sympathetic block (Gilbert and Hultman 1989). Paravertebral blockade can be performed either percutaneously or intraoperatively under visual control to avoid complications.

The efficacy of a continuous paravertebral block with 0.5% bupivacaine on postthoracotomy pain was investigated in 56 patients undergoing thoracotomy. Paravertebral blockade provided significantly better pain relief and pulmonary function with less papaveretum consumption after thoracotomy during the first 48 hours (bupivacaine group: 14 mg versus control group: 136 mg) (Sabanathan et al. 1990).

Continuous epidural and paravertebral blocks, commenced before operation as a part of a balanced analgesic regimen, were both effective for postoperative pain in patients undergoing posterolateral thoracotomy. However, cumulative morphine consumption in the first and second 24-h periods was significantly higher in the epidural group compared with that in the paravertebral group. Patients in the paravertebral group had significantly lower VAS pain scores both at rest and on coughing (Richardson et al. 1999). In a study in 30 patients undergoing anterolateral thoracotomy paravertebral and thoracic epidural analgesia with bupivacaine for postoperative pain treatment were shown to be equally effective in terms of pain relief and recovery of pulmonary function. However, minor differences that would favour paravertebral analgesia were observed (Kaiser et al. 1998). Lignocaine administered for continuous paravertebral nerve blockade after posterolateral thoracotomy has been shown to produce equally good pain control to bupivacaine with less risk of systemic toxicity (Watson et al. 1999).

5.2.2.3 Interpleural analgesia

Reiestad and Strømskag (1986) developed a new method for the treatment of postoperative pain involving intermittent administration of local anaesthetics into the pleural space through an interpleural catheter which was placed using a percutaneous technique. These investigators presented good results in pain relief in the patients undergoing cholecystectomy, renal surgery, and unilateral breast surgery (Reiestad and Strømskag 1986). Interpleural analgesia is induced by injecting the local anaesthetic into the interpleural space which lies between the parietal and visceral pleurae (Reiestad and Strømskag 1986). The parietal pleura is in close proximity to the intercostal nerves anteriorly, laterally, and posteriorly. Interpleural analgesia (previously called intrapleural analgesia) produces regional analgesia of the chest wall and is used for pain therapy in various indications i.e. breast, renal, gall bladder surgery, and chronic pain.

Interpleural analgesia with local anaesthetics has also been used for pain relief after thoracic surgery (Rosenberg et al. 1987, Symreng et al. 1989, Ferrante et al. 1991, Mann et al. 1992, Schneider et al. 1993, Silomon et al. 2000). In this method local anaesthetic agents can be delivered via an indwelling interpleural catheter by intermittent (Mann et al. 1992, Schneider et al. 1993) or continuous infusion (Rosenberg et al. 1987). However, the results of all these studies are controversial.

Continuous interpleural bupivacaine administration using the method developed by Reiestad and Strømskag was unsatisfactory in the management of postoperative pain after thoracotomy. The initial bolus dose and the following infusion of 0.5% bupivacaine were adjusted according to the patient's weight (Rosenberg et al. 1987). In another study, intermittent interpleural 0.25% bupivacaine administered in bolus doses for 48 – 72 hours after posterolateral thoracotomy had no effect on total opioid consumption when the dose of papaveretum was adjusted to the weight of the patients. The bupivacaine group had significantly smaller decreases in FVC and FEV_1 during the follow-up time. Linear analogue pain scores showed reduced postoperative pain in the bupivacaine group at 4, 24 and 72 hours postoperatively compared with the saline group (Mann et al. 1992). Interpleural 0.5% bupivacaine 30 ml compared with interpleural saline administered in bolus doses every 4 h for a total of 12 doses after posterolateral thoracotomy resulted in no differences in VAS pain scores or analgesic requirements. Supplementary morphine or pethidine was given on demand and no PCA was used (Schneider et al. 1993). However, in another study in 83 patients interpleural bupivacaine analgesia had no influence on acute postthoracotomy pain. Patients in the bupivacaine group received 0.5% bupiva-

caine 20 ml and patients in the placebo group received the same amount of saline. Every 4 hours thereafter, each group received the same medication 10 times. The patients were allowed to use i.v. PCA with piritramide for additional pain relief. Mean pain scores were significantly reduced 30 min after interpleural instillation of bupivacaine or saline. However, there were no differences between the groups. The usage of additional piritramide was similar in both groups (Silomon et al. 2000).

5.2.2.4 Epidural blockade

Local anaesthetics can be used alone or in combination with opioids for epidural analgesia (James et al. 1981, Logas et al. 1987, Hurford et al. 1993, Kaiser et al. 1998, Mahon et al. 1999). Epidural analgesia can be performed using either a lumbar or a thoracic approach (Cousins and Veering 1998). The epidural space surrounds the spinal meninges and extends from the foramen magnum to the sacral hiatus. The epidural space is bounded anteriorly by the posterior longitudinal ligament, laterally by the pedicles and the intervertebral foramina and posteriorly by the ligamentum flavum and the anterior surface of the lamina. In addition to the nerve roots that transverse the epidural space, the contents of the epidural space are fat, areolar tissue, lymphatics, arteries, and the extensive internal vertebral venous plexus (Bridenbaugh et al. 1998).

An epidural combination of morphine plus bupivacaine or epidural morphine alone in the treatment of postthoracotomy pain tended to lower self-assessed pain scores compared with epidural bupivacaine, epidural saline and i.m. morphine (Logas et al. 1987). Epidural infusion was started 30 min after the induction of anaesthesia at a rate of 3 ml/h for patients > 60 years of age or shorter than 168 cm, 4 ml/h for all other patients. If any patient with epidural infusion complained of postoperative pain, the rate of the infusion was increased in two successive 1 ml/h increments to a maximal rate of either 5 ml/h or 6 ml/h. Continuous thoracic epidural fentanyl combined with bupivacaine infusion resulted in a significantly lower infusion rate than the rate in the patients receiving lumbar epidural infusion of bupivacaine and fentanyl after lateral thoracotomy. Both techniques were free from major complications (Hurford et al. 1993).

With perioperative thoracic epidural analgesia using a mixture of bupivacaine 0.1% with adrenaline 1:200000 and fentanyl 0.002 mg/ml via the epidural catheter with an average intraoperative infusion rate of 7 ml/h (2 – 15 ml/h) postoperative respiratory parameters remained stable and no opioid-induced respiratory depression was observed. At the end of surgery PCEA was instituted utilising the same epidural solution for postoperative analgesia. No additional i.v. analgesia was administered. Minor adverse effects, especially nausea and vomiting, were seen in less than 15% of the patients in this follow-up study (Schultz et al. 1997). Epidural infusion of bupivacaine 10 or 5 mg/h resulted in improved analgesia during physiotherapy and a significant opioid sparing effect (50% decrease) compared with epidural infusion of bupivacaine 1 mg/h or epidural saline. In this double-blind study (Liu et al. 1995) all patients received a PCEA device with fentanyl as supplementary analgesic.

5.2.2.5 Epidural opioids

Epidural opioids have been administered by the thoracic (El-Baz et al. 1984, Asantila et al. 1986, Logas et al. 1987, Niemi and Breivik 2001) and lumbar (Sandler et al. 1986, Sandler et al. 1992) routes. Anatomic sites of opioid analgesic action are multiple, and include supraspinal areas, the spinal cord, and injured tissue in the periphery. Systemically administered opioids rapidly reach the spinal cord, brainstem, and brain. Epidural opioids are distributed into the bloodstream and reach the periphery, brainstem, and brain in addition to their

spinal target (Bonnet and Baubillier 1993, Carr and Cousins 1998). There are reports showing that epidural and i.v. administration of morphine produced equivalent postoperative analgesia (Sandler et al. 1986).

Thoracic epidural morphine administration resulted in decreased requirements of morphine and the same degree of analgesia when compared with lumbar administration in patients undergoing lateral thoracotomy (Grant et al. 1993).

In a study by El-Baz (El-Baz et al. 1984) analgesia was comparable with intermittent administration of 0.5% bupivacaine through a thoracic epidural catheter and with continuous infusions or intermittent bolus doses of thoracic epidural morphine. In another study lumbar epidural morphine given in a bolus dose of 5 mg on demand resulted in significantly lower total doses of morphine compared with i.v. morphine given in a dose of 0.05 – 0.07 mg/kg on demand in treatment of postthoracotomy pain. The epidural morphine group also had significantly better pain relief during the immediate postoperative period up to 8 hours and improved postoperative pulmonary function compared with the i.v. morphine group. Although the mean respiratory rate was lower in the epidural group, significant respiratory depression did not occur in either group (Shulman et al. 1984).

A dose-response study of lumbar epidural sufentanil bolus doses showed sufentanil to provide rapid and effective analgesia, but with a brief duration of action. Furthermore, increasing the dose resulted in an increased incidence of respiratory depression without any additional analgesic benefit (Whiting et al. 1988). It is noteworthy that sufentanil is the only opioid which has regulatory approval for epidural administration. There are however, numerous studies in which epidural administration of an opioid offered no advantage over the i.v. route.

Lumbar epidural fentanyl for postthoracotomy pain relief provided little if any advantage over i.v. fentanyl infusion (Sandler et al. 1992). In another study, epidural pethidine infusion (0.33 mg/kg/h) for pain management after thoracotomy resulted in significantly better postoperative FEV_1 and FVC values than i.v. pethidine infusion (0.33 mg/kg/h). The epidural group also had significantly lower mean VAS scores and lower total pethidine dosage. Both groups had an i.v. PCA device which was programmed to deliver pethidine in 10 mg boluses with a lockout interval of 5 min (Slinger et al. 1995).

A comparison of thoracic epidural fentanyl with intravenous fentanyl showed that when fentanyl infusions were titrated to the patient's VAS pain ratings, epidural administration produced similar analgesia to the intravenous route but with fewer adverse effects and lower infusion rates. This study supports the suggestion that administration of a highly lipid soluble opioid should be performed in the dermatomal region of the surgical incision (Salomäki et al. 1991).

Epidural opioids and epidural local anaesthetics have been combined with the aim of synergistically blocking spinal nociceptive pathways. Combination of local anaesthetics and opioids can reduce the dose-related adverse effects of either class of agent alone. Several studies have examined the effectiveness of this technique after thoracotomy (Logas et al. 1987, Bigler et al. 1992).

Thoracic epidural bupivacaine plus morphine in combination with rectal administration of either piroxicam or placebo resulted in excellent analgesia with similar needs for supplemental intravenous opioid analgesics in both groups (Bigler et al. 1992).

In the early postoperative period, the addition of bupivacaine 0.1% was shown to improve epidural fentanyl analgesia and was not associated with the disadvantages seen with the addition of bupivacaine 0.2%. VAS pain scores while coughing were significantly higher in patients receiving epidural fentanyl alone compared to those patients receiving additional bupivacaine. The

need for intraoperative vasopressors and the incidence of temporary neurological complications were higher in the 0.2% bupivacaine group (Mahon et al. 1999). Epidural sufentanil analgesia has been shown to be optimal for pain treatment after thoracic surgery when tailored to the site of nociceptive input and combined with bupivacaine (Hansdøttir et al. 1996).

5.2.2.6 Intrathecal opioids

Intrathecal opioids have been used as an adjunct to postthoracotomy analgesia (Gray et al. 1986, Mason et al. 2001). The advantages of the technique are simplicity, reliability and potentially fewer adverse effects from systemic opioid absorption. I.t. opioids are carried rostrally in the cerebrospinal fluid and, compared with epidural opioids, enter the peripheral circulation to a lesser degree (Carr and Cousins 1998). However, this technique has an increased risk of respiratory depression and postspinal headache (Cousins and Mather 1984).

Intrathecal injection of 12 µg/kg morphine resulted in significantly lower pain scores and significantly lower pethidine requirements (59 mg versus 167 mg) compared to control patients treated with i.v. pethidine after thoracotomy. The consciousness level of the patients in the i.t. group was higher than in the control group (Neustein and Cohen 1993). I.t. fentanyl resulted in a faster onset of analgesia and significantly lower pain scores at rest, on coughing and on movement compared with the control groups after posterolateral thoracotomy. The peak expiratory flow rates were also higher in the i.t. fentanyl group. All patients were allowed to use i.v. PCA Mo with a bolus dose of 2 mg and lockout time of 10 min (Sudarshan et al. 1995).

In patients undergoing thoracotomy i.t. sufentanil 20 µg combined with Mo 0.2 mg given after induction of general anaesthesia resulted in lower pain scores and i.v. PCA Mo consumption during the first 24 h compared with the control group (Mason et al. 2001).

In a comparison between i.t. Mo 0.5 mg, 50 µg sufentanil and a combination of the two i.t. Mo provided better postoperative analgesia than the other two medications tested, both at rest and on coughing (Liu et al. 2001). The study was performed in patients undergoing thoracotomy with the tested drugs given before general anaesthesia.

Serious adverse events associated with the spinal techniques are high spinal blockade or significant systemic toxicity after spinal local anaesthetics, respiratory depression after spinal opioids (Etches et al. 1989) and rare cases of spinal cord trauma or nerve trauma, haematoma, infection or inflammatory reaction associated with the introduction of catheter or needle (Bridenbaugh et al. 1998, Carr and Cousins 1998, Cousins and Veering 1998). Other troublesome adverse effects include nausea, pruritus and urinary retention after intraspinal opioids (Bridenbaugh et al. 1998, Carr and Cousins 1998, Cousins and Veering 1998), hypotension, temporary paralysis, urinary retention and paraesthesia after intraspinal local anaesthetics (Bridenbaugh et al. 1998, Carr and Cousins 1998, Cousins and Veering 1998).

5.2.2.7 Other drugs

Epidural clonidine, an α_2-agonist, has the potential for effective antinociceptive activity after systemic or spinal administration (Maze et al. 1988). The mechanism of action appears to be modulation of the endogenous adrenergic receptors in the dorsal horn of the spinal cord. However, there are controversial data regarding the efficacy of clonidine. The efficacy of a single dose of thoracic epidural clonidine 3 µg/kg was compared with saline in a double-blind study, where no analgesic benefits were observed (Gordh Jr. 1988). In another study, addition of 2 µg/kg clonidine to bupivacaine for intercostal nerve blockade for thoracotomy led to a short-term enhancement of postoperative pain control and improvement

of arterial oxygenation. Total opioid consumption for the first 24 hours was significantly lower for the group which received clonidine added to a local anaesthetic solution compared with the clonidine i.m. group (dose 2 µg/kg) (30 mg versus 41 mg) and the control group (30 mg versus 47 mg). Postoperative analgesia was performed with PCA using piritramide. No significant difference in total opioid consumption was noted between the clonidine i.m. group and the control group during the first 24 hours postoperatively (Tschernko et al. 1998).

PCEA with morphine plus ketamine may provide effective analgesia with smaller doses of morphine and fewer adverse effects, compared with PCEA with morphine alone (Tan et al. 1999).

5.2.3 Other methods

Cryoanalgesia involves freezing of an intercostal nerve by intraoperative application of a cryoprobe to its posterior aspect, and then allowing the nerve to thaw (Lloyd et al. 1976, Maiwand and Makey 1981, Maiwand et al. 1986). The procedure may then be repeated and can be performed on several nerves in the dermatomal region of the incision. Because the neurolytic lesion produced is partial, and the endoneurium is preserved, axonal regeneration is possible and normal sensation should return after surgery (Nelson et al. 1974). Concerns have been raised about possible long-term neuralgia (Roxburgh et al. 1987). A two-group study comparing cryoanalgesia with a control group that did not receive cryoanalgesia suggested that there were no advantages associated with the treatment. Approximately 20% of the treated patients developed intercostal neuralgia by 6 weeks after surgery (Müller et al. 1989). Normal sensation returns after three to six months following peroperative cryoanalgesia (Maiwand and Makey 1981).

Perioperative cryoanalgesia of the intercostal nerves was not shown to be beneficial in the control of postthoracotomy pain. After discharge from hospital patients were seen about six weeks and six months after operation (Roxburgh et al. 1987).

A significant proportion of patients undergoing thoracotomy showed improvement after percutaneous cryotherapy. However, relief was only temporary and one third of the patients felt that symptoms were exacerbated by the therapy. The follow-up time was 3 months (Conacher 1986). In another study cryoanalgesia provided a slight improvement in postoperative pain and analgesic requirements in patients undergoing thoracic surgery but these effects were not as marked as with high thoracic epidural infusion of bupivacaine and fentanyl. All patients were allowed i.v. buprenorphine 0.3 mg or propacetamol 1g as supplementary analgesics (Brichon et al. 1994).

Transcutaneous electrical nerve stimulation (TENS) was introduced into clinical practice in 1972 as an adjunct to other therapies. Since then it has been used for postoperative pain relief, including after thoracic operations. TENS may produce analgesia by modulation of nociceptive input in the dorsal horn of the spinal cord through peripheral electrical stimulation of large sensory afferent nerves, the so-called gate control theory of pain (Wall 1985). Alternatively, electrical stimulation of certain receptor sites in the dorsal horn of the spinal cord may release endorphins. Endogenous opioid and nonopioid (e.g., γ-aminobutyric acid) mechanisms may be involved in mediating TENS-induced analgesia (Brodsky and Mark 1997). The only significant adverse effects are local skin hypersensitivity and the possibility that the electrical current could interfere with the function of cardiac pacemakers. On the basis of the available published data TENS is not a reliable pain relief method in the treatment of acute postthoracotomy pain, but can be useful in treatment of chronic postthoracotomy pain (Stubbing and Jellicoe 1988, Benedetti et al. 1997a, Benedetti et al. 1997b, Brodsky and Mark 1997).

5.3 Respiratory and cardiovascular effects of thoracic surgery

Significant changes in pulmonary mechanics, gas exchange and control of breathing occur immediately after thoracic surgery and anaesthesia (Hachenberg and Pfeiffer 1999). Opioids, which are commonly used for treatment of postoperative pain, suppress the spontaneous activity of the respiratory centres thus further decreasing respiratory drive (Craig 1981).

The typical respiratory effect after thoracic surgery is ventilatory restriction, in which there is a moderately decreased inspiratory volume and vital capacity as well as a small but important decrease in functional residual capacity. In this situation the patients breathe rapidly with small tidal volumes and are unable to take deep breaths. In addition, the patients are unable to cough properly because of the diminished inspiratory capacity (Craig 1981). Immediately after lateral thoracotomy the reduction in peak flow rates and timed forced expiratory volumes is of the order of 75% (compared with preoperative values) (Coleman 1987). If a restrictive pattern of ventilation with reduced lung compliance develops, hypoxemia may result from shunting of pulmonary arterial blood through atelectatic areas of the lung leading to ventilation/perfusion imbalance (Conacher 1990).

Postoperative disturbances in gas exchange have many causes (Hachenberg and Pfeiffer 1999). Immediately after surgery and anaesthesia there is hypoxemia lasting from few minutes up to a couple of hours. This early hypoxemia is considered to be a consequence of anaesthesia rather than factors influenced by pulmonary mechanics (Spence 1982). Other possible mechanisms include alveolar hypoventilation, ventilation/perfusion disturbances, and decreased cardiac output and increased oxygen consumption due to increased muscle tone as well as shivering. The patients with disturbances in gas exchange are unable to take deep breaths after surgery. Typical for this disturbance is hypoxemia without hypercarbia (Craig 1981). However, these effects are not caused solely by perception of pain. Other underlying causes include lung trauma, altered architecture, local pulmonary oedema, increased airways resistance and respiratory muscle dysfunction (Conacher 1990).

Disturbances in respiratory control in the immediate postoperative phase are mainly due to intraoperative anaesthetics including drugs used for maintenance of anaesthesia and analgesia. Later, opioid analgesics used for pain treatment may influence respiratory control (Catley 1984). If pain treatment is inadequate, the patient is unable to breathe sufficiently deeply (Conacher 1990). Due to shallow breathing some parts of the lung can collapse leading to atelectases. At the same time the patient is unable to cough and the retention of sputum can lead to an increased risk of pneumonia (Conacher 1990, Goldstraw 1995).

Hypoxemia leads to global hypoxic pulmonary vasoconstriction (HPV). This is a physiological mechanism that constricts the pulmonary vessels in those areas which are not well ventilated. HPV is mediated by low alveolar oxygen tension as well as by low oxygen tension in mixed venous blood. In chronic pulmonary diseases, HPV is responsible for cor pulmonale and right ventricular failure (Enson 1977). After pulmonary resection, especially after whole lung resection, the total blood volume perfusing the remaining lung is relatively increased. The combination of HPV and increased blood volume overstrains the right side of the heart and atrial fibrillation may occur postoperatively (Currens et al. 1943, Lindgren et al. 1991).

Incidences of atrial fibrillation as high as 20% have been reported after left sided thoracotomies. Prophylactic verapamil and digitalis therapy has been shown to protect the right ventricle against HPV and prevent atrial tachyarrhythmia in the immediate postoperative period (Lindgren et al. 1991).

Myasthenia gravis patients often undergo sternotomy when their thymus is re-

moved for treatment of the disease. These patients are particularly vulnerable to adverse respiratory events postoperatively as their respiratory muscles are often weak and the pulmonary reserves diminished. In addition, myasthenia gravis patients are extremely sensitive to respiratory depression associated with opioids, which explains why postoperative pain treatment can be problematic in these patients (Baraka 1992).

5.4 Chronic pain after thoracotomy

Persistent postthoracotomy pain is common but its true incidence is difficult to assess (Jackson 1993). The reported incidence is 29 – 67% (Matsunaga et al. 1990, Perkins and Kehlet 2000), of which only 25% is severe (Kanner et al. 1982). Long-term postthoracotomy pain has been reported after surgery for both malignant as well as benign disease (Kanner et al. 1982, Dajczman et al. 1991). In thoracotomy patients with malignancy, however, the duration of postoperative pain was found to last longer (Kanner et al. 1982). Decreased severity of chronic pain has been reported after VATS when compared with lateral thoracotomy (Landreneau et al. 1994) and after posterolateral thoracotomy the severity of chronic pain is increased when compared with anterolateral thoracotomy (Nomori et al. 1997, Benedetti et al. 1998). Patients undergoing VATS appear to have less subjective shoulder dysfunction than patients undergoing thoracotomy (Landreneau et al. 1994). There is little data available concerning the relationship between the immediate postoperative pain treatment and long-term postthoracotomy pain (Katz et al. 1996, Obata et al. 1999).

The morbidity and the nature of residual pain after thoracotomy for malignant and benign disease was investigated in 90 patients 6 – 18 months after the thoracotomy. Two patients in three complained of postthoracotomy pain for up to 6 months, but 75% of these patients regarded their pain as mild and needed no medication. The residual pain persisted longer in patients with malignancies, in patients aged over 50 years and in patients who needed analgesics for more than two postoperative weeks (Matsunaga et al. 1990).

The predictors of the postthoracotomy pain syndrome (PTPS) when tumour recurrence is excluded include the extent of acute postoperative pain and intercostal nerve dysfunction. These results are based on a computerised search of the medical literature covering the entire database from 1966 through most of 1998 concerning chronic pain as an outcome of surgery. Only thoracotomy studies with more than 50 patients per study were included in this analysis. In addition, the studies had to contain data about persistent pain (12 weeks or more after surgery). Six thoracotomy studies fulfilled these inclusion-exclusion criteria. These studies assessed together 878 patients, of whom 417 (47%) had PTPS (Perkins and Kehlet 2000).

An incidence of 26% (n = 126) for persistent or recurrent pain has been reported in a prospective follow-up study after thoracotomy. During the monthly follow-up for over 8 months the pain had disappeared at 5 months in 79 patients but returned in 13 patients while in 20 patients the pain actually increased in severity. The pain was caused by either tumour or infection (Kanner et al. 1982).

In another study with a median follow-up time of 19.5 months (2 months – 5 years) the incidence of long-term postthoracotomy pain was reported to be 54%. Pain intensity was mostly low but 23% of the patients stated that pain interfered with their life to some extent. Persistent pain appeared to decrease with time. One year after surgery its incidence was 55% whereas two years after surgery it was 45% and more than three years after surgery it had decreased to 38% (Dajczman et al. 1991).

In a small, but well designed prospective study of pre-emptive, multimodal anal-

gesia Katz and co-workers reported long-term pain in 52% of the patients who had undergone lateral thoracotomy 1.5 years earlier. The patients were interviewed by telephone using a standardised questionnaire. The typical description was of a dull, aching or burning pain situated in the chest wall. Early postoperative pain was the only factor that significantly predicted long-term pain. Pain intensity on the first day after surgery, both at rest and after movement, was significantly greater among patients who developed long-term pain compared with those who did not. Cumulative Mo consumption was identical for the two groups, indicating that differences in pain were not mediated by postoperative analgesic usage (Katz et al. 1996).

Postthoracotomy pain may also be of nonneuropathic origin. In a retrospective study 27 patients with PTPS were followed in a pain clinic. The first consultation about the patient's pain was on average 75 days after surgery. Mechanical allodynia was seen in 41% and hypesthesia in 93% of patients. Two types of trigger points were found; the first, adjacent to the wound, was observed in 44% of the patients, while the second, observed in 67% of the patients, was in the scapular region in a taut muscular band. The trigger point in a taut muscular band met the clinical criteria of myofascial pain and it was effectively treated with injections using local anaesthetics (Hamada et al. 2000).

The effect of a continuous epidural block initiated before thoracic surgery on early and long-term pain was investigated in a double-blind study in 70 patients undergoing posterolateral thoracotomy. After induction of anaesthesia the patients were randomly allocated to one of the two groups. In the preoperative group, 4 ml mepivacaine 1.5% was administered epidurally 20 min before the surgical incision, followed by a continuous infusion at 4 ml/h until 72 hours after surgery. For the postoperative group the procedure was the same except that the first 4-ml dose was administered at completion of the operation. If pain relief was inadequate 50 mg indomethacin p.r. was administered on request. No other analgesics were administered. The VAS scores at rest were lower in the preoperative group at four hours after surgery and on the second and third postoperative days. There was no difference between the groups in the usage of rectal indomethacin up to the seventh postoperative day. The percentages of pain-free patients were higher in the preoperative group at three and six months after surgery (Obata et al. 1999).

6 AIMS OF THE STUDY

The aims of the present study were

1. To investigate the incidence, severity and duration of acute postthoracotomy pain (I).

2. To compare the efficacy and adverse events of intravenous morphine, nonsteroidal anti-inflammatory analgesics and three different regional anaesthetic methods in pain relief after two types of thoracic surgery (II, III, IV).

3. To compare the efficacy and adverse events of intravenous and intrathecal morphine in pain relief after transsternal thymectomy in myasthenia gravis patients (V).

4. To investigate the incidence, duration, severity and risk factors of persistent postthoracotomy pain (I, VI).

7 PATIENTS AND METHODS

7.1 Patients

A total of 442 patients were examined in six different studies. The 207 patients reported in paper I had undergone thoracotomies at Helsinki University Central Hospital during 1986 – 1988. The 110 consecutive patients reported in paper VI underwent elective thoracotomy at Helsinki University Central Hospital during 1991 – 1994. The 125 patients participating in the studies reported in papers II – V underwent thoracic surgery at Helsinki University Central Hospital during 1989 – 1996.

In study I, the charts of all 214 patients undergoing thoracotomy during the period in question were examined to determine the amount of analgesics the patients were prescribed and how much they actually received during the first two postoperative days. Of the total of 214 medical records, seven were excluded because the patient had either died or had renewed surgery within the first 2 postoperative days. A letter was sent to 150 surviving patients (Table 1). The characteristics of all patients are shown in Table 2. A total of 136 patients entered studies II – V. Eleven patients were excluded from studies II – V mostly for technical reasons (Table 3).

Table 1: Number of patients in study I

Patient documents studied	214
Patients excluded (reoperation or death within first 2 postoperative days)	7
Medication analysed	207
Questionnaire sent	150
Questionnaire answered	134
% of patients answered the questionnaire	89%

Table 2: Demographic data of all patients in studies I – VI

The data is presented as arithmetic means (range).

Paper	*I*	*II*	*III*	*IV*	*V*	*VI*
Study design	Retrospective	randomised, double-blind, placebo controlled, parallel-group	randomised, open, parallel-group	randomised, double-blind, placebo controlled, parallel-group	randomised, open, controlled, parallel-group	prospective, follow-up
Number of patients	207	30	45	30	20	110
Female/male	69/138	6/24	23722	16/14	17/3	45/65
Age (y)	57.2	57.2 (23–75)	51.5 (23–72)	45.3 (18–70)	35.2 (16–81)	56.3 (19–77)
Weight (kg)	71.9	74.8 (40–105)	75.8 (52–112)	76.0 (56–116)	68.5 (50–110)	73.3 (44–127)
Height (cm)	NA	174 (159–185)	171(154–196)	170 (155–189)	167 (150–182)	169 (148–190)
ASA	I–IV	I–III	I–III	I–III	II–III	I–IV
Duration of operation (min)	NA	112 (30–205)	91 (25–205)	58 (20–265)	78 (48–170)	NA
Type of operation						
Pneumectomy	42	5	3	–	–	21
Lobectomy	151	17	17	–	–	34
Biopsy, resection	13	8	25	30	–	55
Thoracolaparotomy	1	–	–	–	–	–
Thymectomy	–	–	–	–	20	–
Malignant disease	84%	80%	51%	17%	0%	57%
Benign/malignant disease	NA	6/24	22/23	25/5	20/0	47/63

NA = not available

Table 3: Patient numbers in studies II – V

Study no.	II	III	IV	V
No. of patients entered the study	NA	51	35	20
No. of patients analysed	30	45	30	20
No. of patients excluded from the study	NA	6	5	0
massive haemorrhage		1	2	–
catheterization unsuccesful		2	–	–
unable to cooperate		1	–	–
severe nausea before operation		1	–	–
study infusion stopped too early		–	1	–
difficulties with oxygenation during the operation		–	1	–
operation type changed		1	1	–

NA = not available

In studies II – V, patients with clinically manifest cardiac, hepatic or renal failure were excluded, as well as patients with allergy to morphine or the study drugs i.e. local anaesthetics or nonsteroidal anti-inflammatory analgesics. Mentally confused patients were also excluded from the studies. In studies II – V, the patients had to be ASA Physical Status I – III. In studies II – IV, the patients had to be younger than 75 years. In study III, patients scheduled for pleurectomy or unable to cooperate, patients with a neurological disease or infection at the operation site and patients who had a preoperative forced expiratory volume (FEV_1) of less than 60% of the reference value were also excluded. In studies II and IV, patients with a history of gastrointestinal bleeding or peptic ulceration, haemorrhagic diathesis or asthma were excluded. In study II the estimated postoperative FEV_1 had to be > 1.0 l/sec. In study III, patients with a preoperative FEV_1 below 60% of the reference value, indicating severe pulmonary dysfunction, and patients with known sleep apnoea were also excluded as well as patients with back complaints or skin infections in the lumbar region.

Twenty patients with a diagnosis of myasthenia gravis who were scheduled for transsternal thymectomy were included in study V. The diagnosis of myasthenia gravis had been confirmed by a typical history, characteristic neurophysiologic findings (EMG), the presence of acetylcholine receptor antibodies (anti-AChR-ab) and/or positive response to edrophonium. Acetylcholine receptor antibodies were determined by radioimmunoassay (Lefvert et al. 1978). Titres, expressed as arbitrary units l^{-1} were considered abnormal when over 0.2. In addition, all patients had undergone human leukocyte antigen (HLA) typing. The clinical severity of myasthenia gravis was determined using a modified Osserman's classification after testing the fatigability of different muscle groups (Oosterhuis 1984). Anticholinesterase medication was withdrawn 12 h preoperatively and started again 24 h postoperatively.

In study VI, 110 patients were interviewed one day before elective thoracic surgery. The patients also completed a questionnaire 5 – 7 days after surgery. A standard mail interview was performed 3, 6 and 12 months after surgery. Reminders were posted two weeks after the first letter if necessary. All consecutive patients were studied except those who died within one week after surgery (Table 4).

Patients having an epidural or a paravertebral catheter or PCA for postoperative pain treatment as well as those who were reoperated within one week were excluded from the analgesic usage part of the study. However, their data were used to analyse the incidence of chronic postthoracotomy pain. The pain treatment of 83 patients was analysed (Table 5).

Table 4: Patient numbers in study VI

	Preoper	1 week	3 months	6 months	1 year
No. of patients who returned the questionnaire	110	100	87	77	67
No response	0	4	11	13	15
No. of patients alive	110	104	98	90	82
Exitus (cumulative count)	0	6	12	20	28
Total	110	110	110	110	110
% of patients who answered the questionnaire (calculated from patients alive)	100%	96%	89%	86%	82%
% of patients who died	0	5%	11%	18%	25%

Table 5: Pain treatment analysis in study VI

	1 week	3 months	6 months	1 year
No. patients alive	104	98	90	82
No. of patients who returned the questionnaire	100	87	77	67
Patients having				
PCA	10	10	9	9
epidural	1	1	1	1
reoperation within 1 week	1	1	0	0
reoperation within 1 week + PCA	1	1	1	1
reoperation within 1 week and paravertebral	1	1	1	1
Subtotal	14	14	12	9
Total no. of patients possible to analyse for pain treatment	86*	73	65*	58
Total no. of patients analysed for pain treatment	83*		63*	

* Results for totals may not agree with results for individual cells because of missing values for split variables (patients have not answered the questionnaire properly)

7.2 Study designs

Study I was a retrospective questionnaire study evaluating the incidence and treatment of both acute and persistent postthoracotomy pain. Study VI was a follow-up study assessing the incidence, duration and severity of persistent postthoracotomy pain. Study III was a randomised, open study designed to assess the efficacy and adverse effects of three different local anaesthetic methods in postoperative pain relief after thoracotomy. Studies II and IV were randomised, double-blinded, placebo-controlled trials. They were designed to assess the efficacy and adverse events of non-steroidal anti-inflammatory drugs in pain relief after thoracic surgery. Study V was a randomised, open study designed to assess the efficacy and adverse events of i.t. Mo in pain relief after sternotomy in patients with myasthenia gravis.

7.3 Anaesthesia (studies II–V)

Due to the retrospective nature of study I details of premedication and anaesthesia could not be obtained from the source data of the patients. In study VI choice of the method of premedication and anaesthesia was left to the discretion of the anaesthetist in charge of the patient. The routine method of postoperative pain relief consisted of intraoperative intercostal blockade with bupivacaine and postoperatively administered parenteral opioids and non-steroidal anti-inflammatory drugs when needed. Patient-controlled analgesia and epidural/paravertebral analgesia were also used, but only in a few patients.

In the interventional studies II – V intramuscular Mo was used as premedication about 1 h before surgery (studies II – IV: 0.13 mg/kg, study V: 0.1 mg/kg). Anaesthesia was standardised in studies II – V. Peroperative monitoring consisted of intra-arterial pressure, pulse oximetry and end-tidal CO_2. In study V electromyography and hand skin temperature were also monitored. Glycopyrrolate 0.2 mg i.v. (study II: 4 µg/kg) was administered immediately before induction. After precurarisation with pancuronium bromide (15 µg/kg) general anaesthesia was induced with fentanyl (0.003 mg/kg) (studies II – IV) or alfentanil (1 – 2 mg) (study V) and thiopentone. Succinylcholine (1.5 mg/kg) was given to facilitate endobronchial intubation (Robertshaw® or Bronchocath® tubes in studies II – IV). The patients in studies II – IV received fentanyl only at the induction of anaesthesia and thereafter no additional opioids were given during anaesthesia, which was maintained with 50% (studies II – III) or 60% nitrous oxide (study IV) and 1 – 3% enflurane in oxygen. In study V anaesthesia was maintained with 66% NO_2 in O_2 without inhalational anaesthetics and additional doses of alfentanil (0.5 – 1 mg) were given if needed up to the start of the closure of sternotomy. In studies III and IV the inspired oxygen concentration was increased to 100% during one-lung ventilation and in study II according to arterial blood-gas analysis to maintain adequate oxygenation. End-tidal carbon dioxide ($ETCO_2$) was monitored continuously and arterial blood samples for determination of arterial blood-gas analyses were obtained at least every 30 min to maintain normo-ventilation. Anaesthesia and postoperative pain treatment of all patients were managed by the same anaesthesiologists (K.P. in study II and III, K.P. or E.N. in study IV, K.P. and E.N. in study V).

Muscular relaxation was achieved with pancuronium bromide and monitored visually using a peripheral nerve stimulator (studies II – IV). At the end of anaesthesia the residual muscle relaxation was antagonised with neostigmine 2 mg and glycopyrrolate 0.4 mg i.v.

In study V neuromuscular function was monitored by EMG of the adductor pollicis muscle (train-of-four stimuli at 20-sec intervals; Relaxograph™ Datex, Finland). In this study an individual dose-response curve for vecuronium was established (Nilsson and Meretoja 1990). At the end of surgery the

neuromuscular block was antagonised with neostigmine 0.06 mg/kg together with glycopyrrolate 0.008 mg/kg divided into three doses and given at 5-min intervals. The patients were extubated when the EMG showed complete recovery and the patients fulfilled the extubation criteria (Gorback 1990).

In studies II and III pulmonary surgery was performed through a standard anterolateral thoracotomy via the 5th intercostal space. In study IV pulmonary surgery was performed using standard thoracoscopy procedures. Three intercostal ports (diameter 5 – 12 mm) were used for insertion of the thoracoscope and the instruments into the pleural cavity (Salo 1994).

7.4 Treatment of post-operative pain (studies II–V)

In study II the patients were randomly allocated to receive either a diclofenac or a placebo infusion in a double blind fashion and the infusion was started immediately after the patient had arrived in the recovery room. In study IV the patients were randomly allocated to receive a diclofenac, a ketorolac or a placebo infusion in a double blind fashion. In this study the infusion was started approximately one hour before anaesthesia. A recovery room nurse who was not otherwise involved in the study prepared the infusions. All infusions were given via an infusion pump (study II: Oximetrix Inc., Mountain View, Ca.; study IV: Terufusion Syringe Pump Model STC521, Terumo© Corporation, Tokyo, Japan).

In studies II and IV the diclofenac infusion (1 mg/ml in 0.9% NaCl) was started with a bolus dose (in study II 25 ml in 15 min and in study IV 17 ml in 30 min) and continued with a constant rate infusion of 2 ml/kg/24 h for 48 h. The maximum daily dose of diclofenac was 150 mg. In study IV ketorolac infusion (0.6 mg/ml in 0.9% NaCl) was started with a bolus dose of 17 ml (= 10 mg) in 30 min and continued thereafter at a constant rate of 2 ml/kg/24 h for 48 h. The maximum daily dose of ketorolac was 90 mg. Placebo infusion (0.9% NaCl) was performed in the same manner, the patients first receiving bolus doses of 25 ml in 15 min (study II) or 17 ml in 30 min (study IV) and the infusion then being continued at a constant rate of 2 ml/kg/24 h for 48 h.

In study III, the patients were randomly allocated to three groups: intercostal, epidural or paravertebral. In the intercostal group, intrathoracic unilateral intercostal nerve blocks (T3 – T7) with a total of 16 ml 0.5% bupivacaine were performed by the surgeon at the end of the operation before wound closure. In the epidural group a thoracic 20-gauge epidural catheter was introduced preoperatively between the 5th and 6th or 6th and 7th spinal processes through an 18-gauge needle (epidural catheter set; Portex®, Hythe, Kent, U.K.) using the midline technique. The correct location of the catheter was confirmed with 4 ml of 2% lignocaine. In the paravertebral group the surgeon placed a paravertebral catheter (epidural catheter set; Portex® Hythe, Kent, U.K.) intraoperatively. Before closure of the thoracotomy wound the catheter was inserted into the pleural cavity percutaneously via an 18-gauge needle at the midclavicular line in the second intercostal space. The parietal pleura was opened (length 1 cm) over the sympathetic trunk at the level of the 3rd rib and an extrapleural pocket fashioned between the posterolateral pleura and the chest wall. It extended from the posterior wound margin on the vertebral bodies to two intercostal spaces above and two below the thoracotomy incision. The catheter was fixed with absorbable suture material (Catgut; Ethicon®, Norderstedt, Germany) close to the sympathetic trunk and the opening in the parietal pleura was closed.

The patients in the epidural and paravertebral groups in study III received bolus doses of 0.25% bupivacaine according to height (8 ml for 150 – 160 cm, 10 ml for 161 – 180 cm and 12 ml for over 180 cm) before wound closure and a continuous infusion

of 0.25% bupivacaine (4 ml/h for 150 – 160 cm, 6 ml/h for 161 – 180 cm and 8 ml/h for over 180 cm) was started immediately after the patient had arrived in the recovery room. The infusion was continued for 48 h using an infusion pump (IVAC Syringe Pump Model 700; IVAC© Corporation, San Diego, CA, USA). In 10 patients in the epidural group and 8 patients in the paravertebral group the position of the catheter was determined by X-ray with contrast medium (4 ml Omnipaque 300 mg/ml, Nycomed Imaging AS, Oslo, Norway).

In study V the patients were randomised to two groups for postoperative pain relief: an intrathecal morphine group (i.t. Mo) and a PCA morphine group (PCA Mo). In the i.t. Mo group the patients were given 10 µg/kg of preservative-free morphine diluted in 2 ml of saline intrathecally before induction of anaesthesia. The injection was performed at the L3 – L4 interspace with a 25 or a 27-gauge Quincke type spinal needle with the patient in a sitting position.

In studies II – V, all patients were also allowed to take supplementary doses of morphine (study II: 10 mg/ml, study III – V: 2 mg/ml) intravenously from a patient-controlled analgesia (PCA) device. In study II the PCA-device (Prominject®; Pharmacia AB, Sweden) was programmed as follows: a bolus dose of 3 mg given over 1 minute followed by a tail dose of 2 mg (continuous infusion of morphine for 60 minutes). The lock out time was 30 minutes. The time points of the self-administered morphine doses were recorded. In studies III – V the PCA-device (Graseby Medical; Graseby Medical Ltd, Colonial Way, Watford, Herts, UK) was programmed to provide a bolus dose of 30 µg/kg corresponding to 2.1 mg of morphine in a patient weighing 70 kg. The lock out time was 5 – 10 min (study IV) or 7 – 10 min (study III, V) up to the first postoperative morning and thereafter 10 – 12 min (study IV), 12 – 15 min (study III) or 15 min (study V). All patients spent the first postoperative night in the postoperative anaesthesia care unit (PACU).

In study II the surgeon performed the intrathoracic intercostal nerve blockades (Th 3 – 7) with 16 ml 0.5% bupivacaine before wound closure. If the morphine dose delivered by the PCA-device was not sufficient for pain relief 5 mg of morphine was given intramuscularly.

7.5 Measurement of pain

Visual analogue scales (VAS) (studies II – V), four point verbal rating scales (VRS: none = 0, mild = 1, moderate = 2 or severe = 3) (studies II – IV), five-point verbal rating scales (none = 0, mild = 1, moderate = 2, severe = 3, excruciating = 4) (study VI) and the McGill pain questionnaire (study VI) were used for pain measurement. For better display of the visual pain intensity scale, a ruler 50 cm long and 10 cm wide with an increasing red area representing pain intensity and a centimetre scale on the back was used (Tigerstedt and Tammisto 1988). In the postoperative pain assessment period, this ruler was shown to the patient from a distance of about 30 cm and the patient asked to indicate with his finger the intensity of his or her pain. The idea behind the VAS and the ruler was explained to the patient preoperatively. In this report of the studies the VAS scores are presented as percentages of the maximum value on the visual analogue scale.

In study II, the patients were asked to assess the intensity of wound pain at rest using a VAS and the intensity of shoulder pain using a VRS. In study III, the patients were asked to assess the intensity of pain at rest and when coughing using a VAS and VRS. In study IV, the patients were asked about the intensity of wound pain at rest, when moving and when coughing using both VAS and VRS. In study V, only a VAS was used to assess the wound pain. The schedule of the examinations is presented in Table 6. It can be seen that there is a long break in the measurements between 6 and 20 hours postoperatively which can be explained by the fact that it was usually the

Table 6: Schedule for the assessment of pain in studies II – V

Time point	*0*	*30 min*	*1 h*	*1.5 h*	*2 h*	*3 h*	*4 h*	*5 h*	*6 h*	*8 h*	*20 h*	*24 h*	*28 h*	*30 h*	*32 h*	*42 h*	*44 h*	*48 h*	*52 h*	*56 h*
Study II	×	×	×	×	×		×		×	×	×	×	×		×		×	×	×	×
Study III			×		×	×	×	×	×		×	×		×		×		×		
Study IV	×		×		×	×	×	×	×		×			×			×			
Study V	×		×		×	×	×	×	×		×	×	×		×		×			

same person who performed the measurements. Additionally, it should be mentioned that due to the timing of the operations, the 6-h measurement was usually performed at 6 p.m. on the day of the operation and the 20-h measurement at 8 a.m. on the first postoperative morning.

In study III, the upper and lower sensory levels of analgesia were assessed by pin prick sensation on both sides. The most caudal and the most cranial dermatomes insensitive to the stimuli were recorded. An observer who was blind as to which infusion the patient was receiving interviewed the patients in studies II and IV. In study VI all patients were interviewed one day before surgery to determine if they had preoperative pain and to familiarise them with the pain measurement questionnaire. Standard methods, i.e. the 5-point verbal rating scale and the McGill pain questionnaire, were used. Patients filled in the pain questionnaire again 5 – 7 days after surgery to evaluate the immediate postoperative pain. The patients were interviewed by a standard letter 3, 6 and 12 months after surgery. Reminders were posted two weeks after the first mailing if necessary.

7.6 Measurement of respiratory, renal and haematological effects

The patients received 28% or 35% oxygen supplementation through a venturi mask until at least 6 hours postoperatively (study IV) or until the first postoperative morning (studies II – III, V). Arterial blood gas analysis was performed in studies II–V up to the second postoperative day. The arterial oxygen pressure values were divided by the inspiratory oxygen fraction (PaO_2/ 0.35) to allow the comparison of values obtained during various oxygen supplementation methods (study II). The schedule of measurements concerning respiratory status is presented in Table 7.

Oxygen saturation was monitored continuously by pulse oximetry (SpO_2) using a finger probe up to the first postoperative morning. In studies III – V forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured with a pocket spirometer (Micro Spirometer; Micro Medical Limited, Rochester, Kent, England). The patient was in a semirecumbent position during measurements and the baseline values were obtained the day before surgery. Respiratory rate (RR) was recorded in studies II – V.

Table 7: Respiratory measurements in studies II – V

	Preoper.	*1 h postop.*	*2 h postop.*	*3 h postop.*	*4 h postop.*	*6h postop.*	*8 h postop.*	*12 h postop.*	*16 h postop.*	*20 h postop.*	*24 h postop.*	*28 h postop.*	*30 h postop.*	*32 h postop.*	*42 h postop.*	*44 h postop.*	*48 h postop.*
Study II																	
Radiospirometry	×																
Chest X-ray	×	×								×						×	
Arterial blood gas analysis	×	×	×		×	×				×							
Respiratory rate	×	×	×	×	×	×				×	×	×		×		×	×
SpO2	×	×	×	×	×	×				×				×			
Study III																	
FEV1, FVC (pocket spirometry)	×		×		×	×				×	×		×		×		×
Chest X-ray		×								×						×	
Arterial blood gas analysis	×	×	×	×	×	×					×						×
Respiratory rate	×	×	×	×	×	×				×	×		×		×		×
SpO2	×	×	×	×	×	×				×	×		×		×		×
Study IV																	
FEV1, FVC (pocket spirometry)	×		×		×	×				×			×			×	
Chest X-ray		×								×							
Arterial blood gas analysis	×	×	×	×	×	×				×						×	
Respiratory rate	×	×	×	×	×	×				×			×			×	
SpO2	×	×	×	×	×	×				×			×			×	
Study V																	
FEV1, FVC (pocket spirometry)	×	×	×	×	×	×		×	×	×	×	×		×		×	
Chest X-ray		×								(×)							
Arterial blood gas analysis	×	×	×	×	×	×	×				×						
Respiratory rate	×	×	×	×	×	×	×	×	×	×	×	×		×		×	
SpO2	×	×	×	×	×	×	×	×	×	×	×	×		×		×	

In studies II and III, urine output was measured up to the second postoperative morning. If the patients had no spontaneous urine output the bladder was catheterised on the first postoperative morning (studies II and III) and, where needed, on the first postoperative evening (study II) or on the second postoperative day (studies II and III).

Crystalloids were infused up to the first postoperative morning in all interventional studies (II – V). In study IV crystalloid solutions were given via an infusion pump in a dose of 40 ml/kg. In studies II and V the amount of crystalloids infused up to the first postoperative morning was not pre-determined in the study protocol. In study III the amount of crystalloids was fixed at 30 ml/kg but the solutions were not given using an infusion pump.

Blood loss during the surgical procedure and postoperatively through the drains was measured (studies II – V). Any loss less than 400 ml (study II) or 500 ml (study III – V) was replaced with hydroxyethyl starch (Plasmafusin 6%®, Kabi Pharmacia AB, Sweden) and any loss exceeding 400 ml (study II) or 500 ml (study III – V) was replaced with packed red cells.

Safety laboratory assessments were performed in studies II – IV according to the schedule presented in Table 8. The effect of i.v. NSAIDs on bleeding time and blood coagulation when administered over 48 hours was of particular interest in studies II and

IV. IVY bleeding time (Simplate-II®; General Diagnostics, Warner-Lambert Co., Morris Plains, New Jersey) was assessed in studies II and IV always by the same person.

The platelet adhesion test (Adeplat S®; Platelet Adhesion Test Set, Semmelweis S.r.l., div. Mascia Brunelli; Milano, Italy) was performed using an in vitro technique in which a certain amount of native blood is passed through a set of glass micro-beads (studies II and IV). The rate of blood flow through the column was kept constant by the use of an infusion pump (Adeplat Pump System). All parameters which influence the retention of platelet by the glass were standardised (Hellem 1970).

Thromboelastography (TEG) (Thrombelastograph D; Hellige GmbH, Freiburg im Breisgau, Germany) was also performed. Samples were citrated whole blood (studies II and IV). Coagulation was initiated by adding calcium chloride to the cuvettes. TEG tracings were analysed by measuring reaction time (R, min), coagulation time (K/R+K, min) and maximum amplitude (MA, mm) (Spiess et al. 1988, Kuitunen et al. 1991).

Table 8: Schedule for laboratory assessments in studies II – IV

	Preoper.	1 h postoper.	2 h postoper.	8 h postoper.	1st postop.day	2nd postop. day	3rd postop. day
Study II							
Hb, Hct	×	–	×	–	×	×	×
Serum creatinine	×	–	–	–	×	–	–
Platelet count	×	–	×	×	×	×	×
IVY bleeding time	×	–	×	×	×	×	×
Adeplat, TEG	×	–	×	–			
Study III							
Hb, Hct	×	×	–	–	×	×	–
Serum creatinine	×	–	–	–	×	×	–
Study IV							
Hb, Hct	×	×	–	–	×	×	–
Serum creatinine	×	×	–	–	×	×	–
Platelet count	×	–	×	–	×	–	–
IVY bleeding time	×	–	×	–	×	–	–
Adeplat, TEG	×	–	×	–	×	–	–

7.7 Measurement of drug plasma concentrations

Plasma drug concentrations were measured in studies III, IV and V. The analyses were performed by the laboratory of the Department of Clinical Pharmacology at University of Helsinki.

In study III, arterial blood samples for assay of plasma bupivacaine concentrations were drawn into siliconised tubes before and 10, 30 and 60 min and 2, 4, 6 and 24 h after the bolus dose of bupivacaine in all groups and, in addition, 48 h after the operation in the paravertebral and epidural groups. Plasma bupivacaine concentrations were determined by high-performance liquid chromatography (Lindberg and Pihlajamäki 1984). Samples were extracted with diethylether. Demethyldoxepin was used as internal standard. The chromatographic system consisted of a C-8 reversed phase column and the mobile phase was acetonitrile – 0.05 mol/l phosphate buffer pH 3.3 (30:70 v/v). The concentration range was linear between 0.020 – 1.5 µg/ml. The coefficient of variation for inter-assay determinations was 3.8% (n = 16) at a concentration of 1.18 µg/ml.

In study IV, arterial blood samples for assay of plasma diclofenac and ketorolac concentrations were drawn into siliconised tubes before and after the 30 min bolus infusion and 30 min, 2, 6, 10, 16, 24 and 48 h after the start of the continuous infusion. Plasma concentrations of diclofenac were determined with high-performance liquid chromatography using electrochemical detection (Zecca et al. 1991). Flufenamic acid was used as internal standard. Samples were chromatographed in a C-18 inverse phase column. The limit of quantitation in the plasma diclofenac analysis was 0.03 mg/l. The coefficient of variation for inter-assay determinations was 1.8% (n = 7) at a concentration of 0.13 mg/l, 5.43% (n = 7) at a concentration of 1.3 mg/l and 1.44% (n = 7) at a concentration of 5.4 mg/l. Plasma concentrations of ketorolac were determined with high-performance liquid chromatography using electrochemical detection (Jones and Bjorksten 1994). Naproxen was used as internal standard. Samples were chromatographed on a C-18 inverse phase column. The limit of quantitation in the plasma ketorolac analysis was 0.05 mg/l. The coefficient of variation for inter-assay determinations was 3.5% (n = 7) at a concentration of 0.08 mg/l, 1.9% (n = 7) at a concentration of 0.8 mg/l and 4.1% (n = 7) at a concentration of 4.0 mg/l, respectively.

In study V, plasma concentrations of morphine were determined with high-performance liquid chromatography using electrochemical detection (Zoer et al. 1986). Dihydromorphine was used as internal standard. Samples were chromatographed in a straight phase system with a silica column. The concentration range was linear between 2 – 40 ng/ml. The coefficient of variation for inter-assay determinations was 13.5% (n = 22) at a concentration of 8 ng/ml. In the PCA-group plasma concentrations of morphine were measured on arrival in the PACU, and 10 min, 30 min, 60 min, 4 hrs and 24 hrs later. In the i.t. Mo group the first plasma concentration of morphine was measured before administration of i.t. Mo followed by measurements 10 min, 30 min, 60 min, 4 hrs and 24 hrs later. The total follow-up period was 48 hours.

7.8 Postoperative evaluation of adverse events and performance status

On the first and second postoperative days the patients in studies II – IV were evaluated for adverse effects (i.e. drowsiness, confusion, nausea, vomiting, itching, abdominal pain, dizziness, hallucinations, difficulties with breathing or allergic reactions) or any other symptom that either the patient or personnel considered important to notify. In study II the axillary temperature was measured preoperatively and on the first, second and third postoperative days

at 4 p.m. At the same time the patients were asked to rate their performance status i.e. sleeping, mobility, drinking, eating and bowel function, using a scale of: absent (0), moderately impaired (1) or normal (2) (study II) or absent (0), moderately impaired (1), slightly impaired (2) or normal (3) (studies III – IV).

7.9 Questionnaire studies

In study I the charts of all 214 patients who had undergone thoracotomies in the IIIrd Department of Surgery, Helsinki University Central Hospital, during 1986–1988 were examined to establish the amounts of analgesics the patients were prescribed and the amounts of analgesics they eventually received during the recovery room period and during the first and second postoperative days on the ward. Nurses' notes were analysed for comments on postoperative pain.

A letter was also sent to the 150 surviving patients asking them to answer the following questions:

1. Would you rate the pain you experienced during the first week after your operation in spite of the painkillers that you were given as minor, considerable or excruciating?
2. Was the pain relief you were given good, satisfactory or poor?
3. If you were not satisfied with the pain treatment, would you have wished for higher doses of analgesics, shorter intervals between doses, local anaesthetic blocks or something else (please specify)?
4. Did you have pain at home?
5. If you had pain at home, did it last for less than 3 months, between 3 and 6 months or for more than 6 months?
6. Do you still have pain that you think is due to the operation?
7. Have you received any treatment for your pain?
8. If you have received treatment, have you been given ordinary pain killers, strong analgesics, other drugs, local anaesthetic blocks, acupuncture, cryotherapy, physiotherapy or something else (please tick as appropriate and specify if necessary)?
9. Could you please indicate the painful area on the enclosed diagram using the following symbols to describe the type of pain: xxx = ache, ooo = burning pain, === = tenderness and III = numbness.

One hundred and ten patients undergoing elective thoracotomy participated in study VI. The amounts of analgesics the patients received were recorded during the first 5 postoperative days. To enable comparison of different analgesics, all opioids were converted to equianalgesic doses of morphine using the ratios presented in Table 9.

Table 9: Equianalgesic doses of opioid analgesics for postoperative pain treatment used in study VI

Morphine	10 mg
Oxycodone	10 mg
Pethidine	75 mg
Buprenorphine	0.3 mg
Codeine	130 mg
Dextropropoxyphene	300 mg

The doses of the nonsteroidal anti-inflammatory drugs (NSAIDs) are presented in Table 10 as fractions of the recommended maximum daily doses for postoperative pain treatment. If a formulation containing both an opioid and an NSAID was used, both ingredients are shown.

Table 10: Equianalgesic doses of NSAIDs for postoperative pain treatment used in study VI

Acetylsalicylic acid	3000 mg
Paracetamol	3000 mg
Diclofenac sodium	150 mg
Indomethacin	150 mg
Ibuprofen	2400 mg
Ketoprofen	300 mg
Ketorolac tromethamine	90 mg
Tolfenamic acid	600 mg
Metamizole	4000 mg

7.10 Ethical considerations

The Institutional Ethics Committees of the Department of Anaesthesia and Department of Cardiothoracic Surgery at Helsinki University Central Hospital approved the study protocols. Informed consent was obtained from all patients in studies II – VI.

7.11 Statistical analysis

A nurse who was in no way involved in the studies performed the randomisation using sealed envelopes. In the double-blind studies the code was opened after the clinical phase of the study. In drug concentration analyses the laboratory personnel was blinded to the samples.

Demographic data was evaluated with Student's t-test (study I – II, VI), with the Kruskal-Wallis (study III – IV) and with the Mann-Whitney test (Study V) where appropriate.

A two-way analysis of variance for repeated measures and Scheffe's method (study II – IV) or Fisher's PSLD test (study V) for testing all contrasts were used for the evaluation of VAS data and consumption of morphine (studies II – V), VRS, (studies II – IV) PaO_2/FiO_2, $PaCO_2$, IVY-bleeding times and platelet counts (study II, IV), bupivacaine concentrations and forced expiratory volume in 1 s (FEV_1) (study III, V) and morphine plasma concentrations and FVC (study V) followed by the Mann-Whitney U-test (study II, V) or the Kruskal-Wallis test (study III) at individual time points, where needed (Table 11).

In study IV, a factorial analysis of variance was used for the statistical analysis of morphine consumption after logarithmic transformation of the data followed byt-tests at individual time points where needed.

Urine output, plasma creatinine, blood loss, platelet count (studies II – IV) and platelet adhesion test values (study II, IV) were analysed in study II using the Mann-Whitney U-test for unpaired data and with the Wilcoxon signed rank test for paired data and in studies III – IV with the Kruskal-Wallis test.

In study V, linear regression analysis was performed to evaluate the relationship between duration of the disease (yrs), preoperative dose of pyridostigmine (mg), anti-AChR-ab-titres (arbitrary units l^{-1}) and individual ED_{95} dose of vecuronium.

The incidence of adverse events (study II – V) and the performance status (study III) were compared using the chi-square test. $P < 0.05$ was considered statistically significant (studies II – III).

In study I, the consumption of analgesics, estimations of pain and pain relief were compared with the Mann-Whitney's U-test, Kruskal-Wallis and Spearman rank correlation test. In study VI, the consumption of analgesics and the degree of pain were analysed by factorial ANOVA. The calculations were performed using the commercially available statistical program StatView 512+ or 4.0 for Macintosh.

Table 11: Statistical analysis

	Study I	Study II	Study III	Study IV	Study V	Study VI
Demographic data	t-test	t-test	Kruskal-Wallis	Kruskal-Wallis	Mann Whitney	t-test
VAS, VRS		2-way ANOVA for repeated measurements followed by Mann-Whitney when needed	2-way ANOVA and Scheffe's method followed by Kruskal-Wallis, when needed	2-way ANOVA for repeated measurements and Scheffe's method	2-way ANOVA and Fisher's PSLD test and Mann-Whitney	
Consumption of morphine		2-way ANOVA for repeated measurements followed by Mann-Whitney when needed	2-way ANOVA and Scheffe's method followed by Kruskal-Wallis, when needed	Factorial ANOVA with lognormal transformation and Scheffe's method followed by t-test, when needed	2-way ANOVA and Fisher's PSLD test and Mann-Whitney	
Urine output, plasma creatinine, blood loss, platelet		Mann-Whitney U-test for unpaired data and Wilcoxon signed rank test for paired data	Kruskal-Wallis	Kruskal-Wallis		
Adhesion test values		Mann-Whitney U-test for unpaired data and Wilcoxon signed rank test for paired data		Mann-Whitney U-test for unpaired data and Wilcoxon signed rank test for paired data		
Relationship between duration of the disease (yrs), preoperative dose of pyridostigmine (mg), anti-AChR-ab-titres (arbitrary units l^{-1}) and individual ED95 dose of vecuronium					Linear regression analysis	
Adverse events		Chi-square test	Chi-square test	Chi-square test	Chi-square test	
Performance status			Chi-square test			
Consumption of analgesics, estimation of pain and pain relief (I) or degree of pain (VI)	Mann-Whitney U-test, Kruskal-Wallis and Spearman rank correlation test					Factorial ANOVA

A two-way analysis of variance for repeated measures and Scheffe's method (study II-IV) or Fisher's PSLD test (study V) for testing all contrasts were used for the statistical analysis of VAS and consumption of morphine (studies II-V), VRS, (studies II-IV) PaO2/FiO2, PaCO2, IVY-bleeding times and platelet counts (study II, IV), bupivacaine concentrations and forced expiratory volume in 1 s (FEV1) (study III, V) and morphine plasma concentrations and FVC (study V) followed by Mann-Whitney U-test (study II, V) or the Kruskal-Wallis test (study III) at individual time points, when needed.

8 RESULTS

8.1 Pain intensity and analgesic consumption as a measure of pain

Consumption of morphine in control patients was somewhat lower after thoracoscopy than after thoracotomy. After sternotomy consumption of morphine was even lower than after thoracoscopy (Table 12 and Figure 1). In the two thoracotomy studies II and III PCA morphine consumption in the placebo groups during the first 48 hours was comparable (mean: study II 137.6 mg vs. study III 119.7 mg).

Table 12: Morphine consumption in control patients (studies II – V)

	Cumulative consumption of morphine after first 24 hours		Cumulative consumption of morphine after first 44 hours	
Study no (additional treatment)	*Median*	*Range*	*Median*	*Range*
Study II (intercostal)	70.1	24–156	135.3	35–238
Study III (intercostal)	70.0	24–137	104.0	36–209
Study IV (–)	59.3	12–124	82.8	16–178
Study V (–)	44.8	14–158	60.2	14–214

Figure 1: Consumption of morphine after different types of operations (control patients)

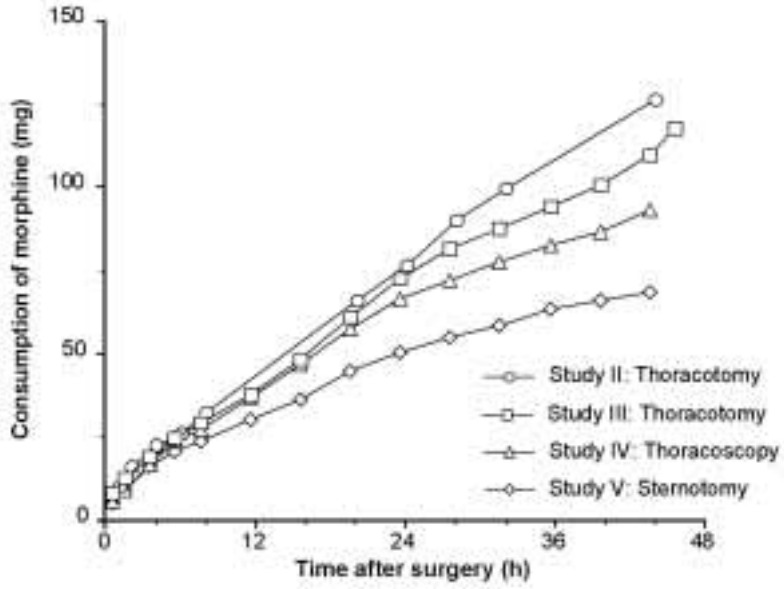


Table 13: Opioid consumption during first 2 days in studies I and VI

	Cumulative consumption of opioids during first 24 hours		Cumulative consumption of opioids during first 48 hours	
	Median	*Range*	*Median*	*Range*
Study I (N = 207)	46	10–138	81	10–188
Study VI (N = 63)	30	0–158	62	7–170

In studies I and VI, consumption of opioids during the first two postoperative days was lower than in studies II – V. In study I cumulative opioid consumption during the first 24 hours was 57 – 61% less than in the thoracotomy studies II – III. In study VI cumulative opioid consumption was 9 – 18% less than in the thoracotomy studies II – III (Table 12 and Table 13).

The VAS-ratings in the control patients after different types of operations are presented in Figure 2 as percentages of the maximum value on the VAS scale (VAS%). There was a significant difference in VAS% between the control patients in studies III and IV ($P < 0.05$) on the first postoperative day and also in studies IV and V ($P < 0.05$) 6 h after the surgery and on the first postoperative day. There was no difference in VAS% between the patients treated with diclofenac for postoperative pain in studies II and IV despite different types of operation (thoracotomy vs. thoracoscopy) and usage of intraoperative intercostal block in study II (Figure 3). In study II, the patients in the control group experienced significantly more wound pain compared with the diclofenac group during the immediate postoperative period (up to 120 min) ($p < 0.05$) and on both postoperative mornings. On the first postoperative morning significantly less ($p < 0.05$) shoulder pain was experienced in the diclofenac group.

Figure 2: VAS% after different types of operations in control patients (studies II – V)

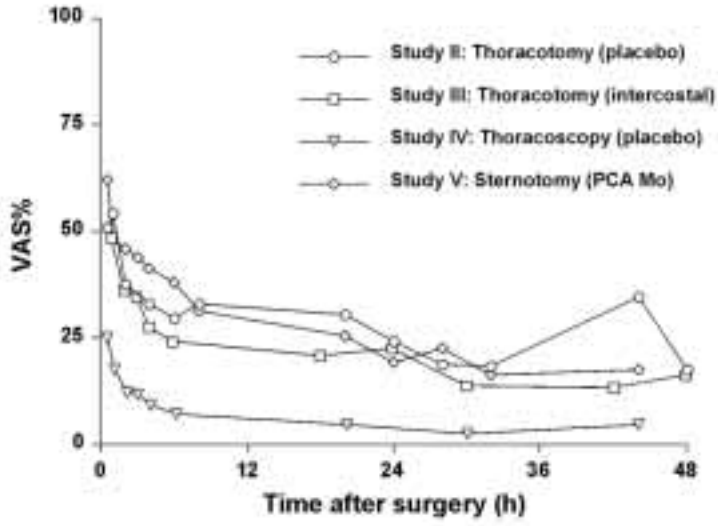
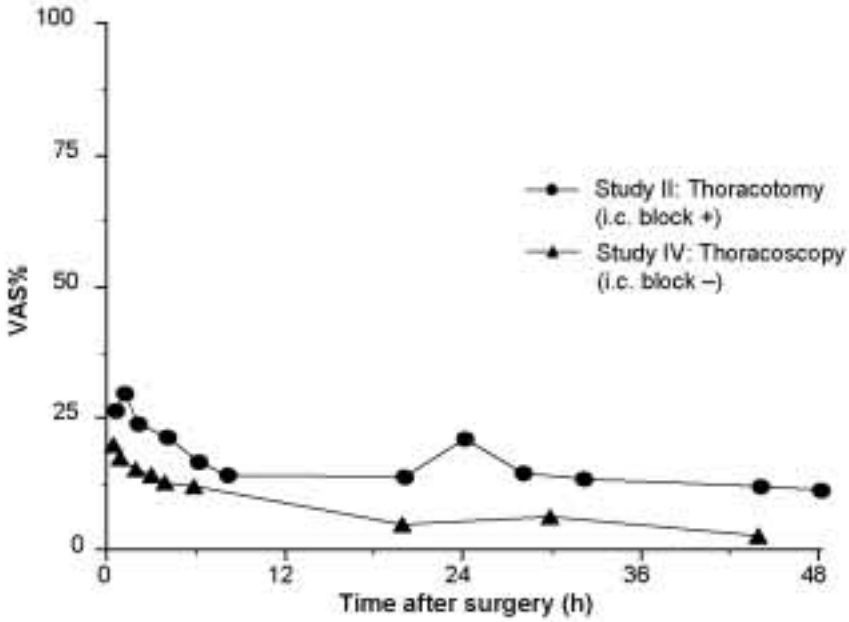
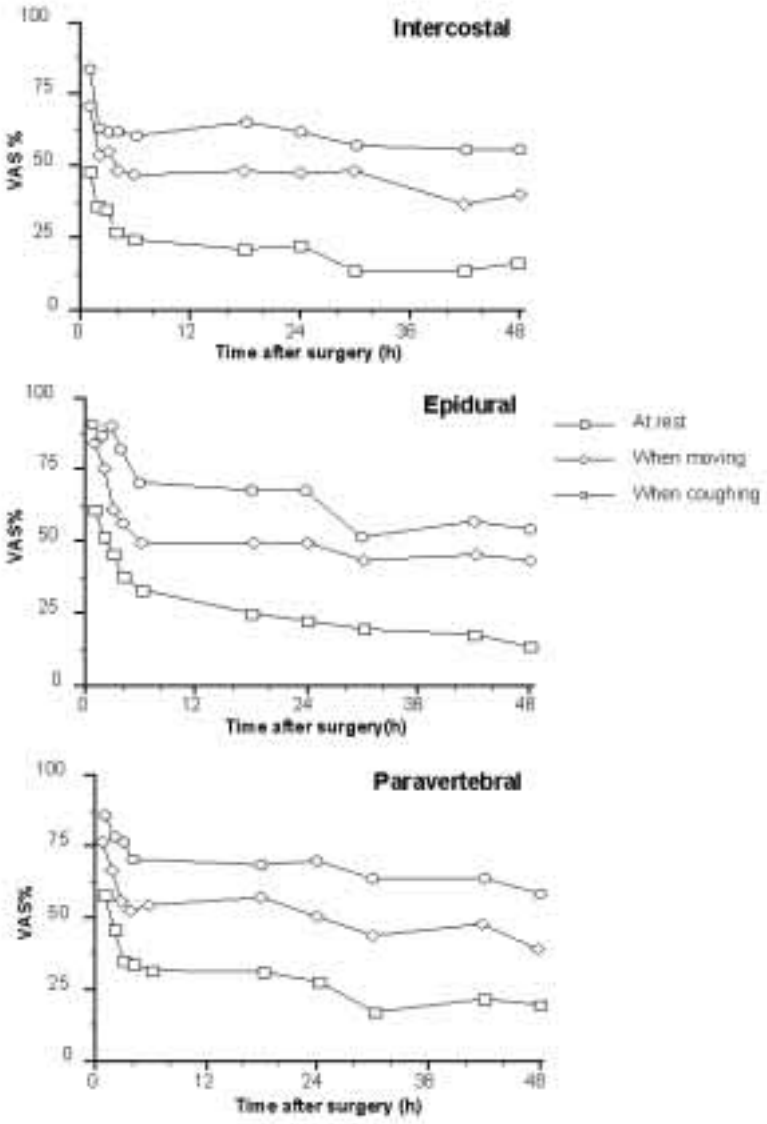


Figure 3: VAS% in patients treated with diclofenac (studies II and IV)



The postoperative VAS pain intensity scores at rest (VAS_{pi}) in the control patients in study III were on average 48% of the maximum value whereas in study IV the average score was 34% (Figure 2). On the first postoperative morning the VAS_{pi} at rest was 22% in study III compared with 9% in study IV. The pain scores were even higher when the patient moved (scores at 24h postoperatively: study III 47% vs. study IV 21%) or coughed (scores at 24-h postoperatively: study III 62% vs. study IV 23%) (Figure 4 and Figure 5). In study III, the patients reported similar levels of pain at rest. In the epidural group, however, the patients experienced significantly more pain when coughing compared with the intercostal group in the immediate postoperative period (up to 4 h) (Figure 4). In study V, the postoperative pain scores at rest were comparable in the i.t. and i.v. Mo groups starting with an average score of 60% of the maximum immediately after surgery and decreasing to 19% of the maximum in 24 hours. The difference in the intensity of pain between the study groups did not increase statistically significantly during the first postoperative day although in the i.t. group 4 patients had postdural puncture headache that exceeded the wound pain in severity.

Figure 4: VAS% in Study III



In study I, 134 surviving patients (i.e. 89%) answered the letter and returned the questionnaire. Of these patients 44% reported that they still had pain which they related to the thoracotomy. There were no comments in 30% of the patients' charts concerning postoperative pain during the two postoperative days on the wards. The charts showed that 10% of the patients had no pain, 40% had pain while severe pain was reported in 20%.

In study VI, 50% of the patients had no pain when admitted home, 37% had pain up to 3 months, 6% for 3 to 6 months, 3% for more than 6 months and 4% could not answer. In this study 17% of all the patients had had pain preoperatively. Neither the incidence nor the severity of chronic pain differed between the patients with malignant and benign disease. Both the incidence and the severity of chronic postthoracotomy pain decreased with time (Table 14).

Figure 5: VAS% in thoracotomy patients (studies II – III)

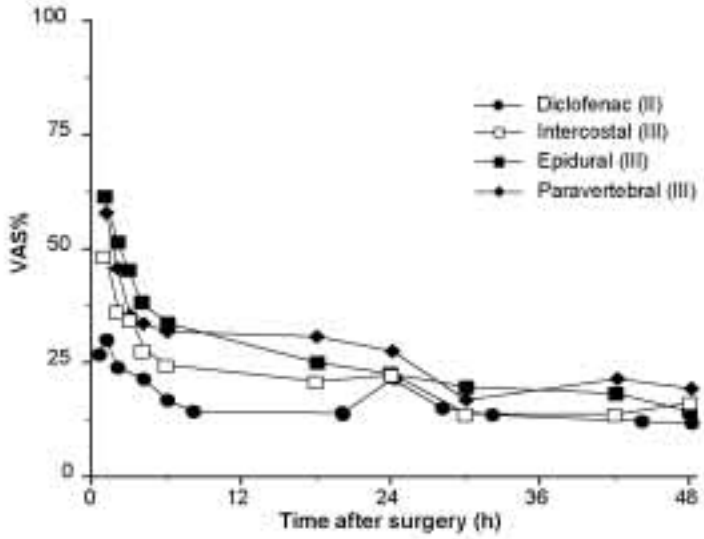


Table 14: Incidence and severity of pain in study VI

	1 week postoperatively		3 months		6 months		1 year	
	n = 97		n = 84		n = 75		n = 62	
	Count	*Percent*	*Count*	*Percent*	*Count*	*Percent*	*Count*	*Percent*
Severity of pain								
No pain	5	5	17	20	19	25	24	39
Mild pain	38	39	38	45	34	45	28	45
Moderate pain	39	40	25	30	20	27	7	11
Severe pain	14	14	3	4	2	3	3	5
Excruciating pain	1	1	1	1	0	0	0	0

8.2 Analgesic efficacy

Only the patients in studies I and VI had intramuscular opioids for pain relief. The distribution of opioid consumption during the recovery room period and the 1st and 2nd postoperative days is shown in Figure 6. In study I, there was a statistically significant correlation between the consumption of opioids in the recovery room and during the 1st postoperative day and between the opioid consumption during the 1st and the 2nd postoperative days. Oxycodone was administered to all patients except to two, who were given morphine as the primary postoperative opioid. In addition, buprenorphine was given to 13 patients (6%) and pethidine to 5 patients (2%). In study VI all patients except two received opioids during the first postoperative day. Most of the patients received oxycodone as the primary opioid analgesic. The amounts of opioids received by the patients are presented in Table 15.

Figure 6: Oxycodone consumption during the first 2 days in studies I and VI

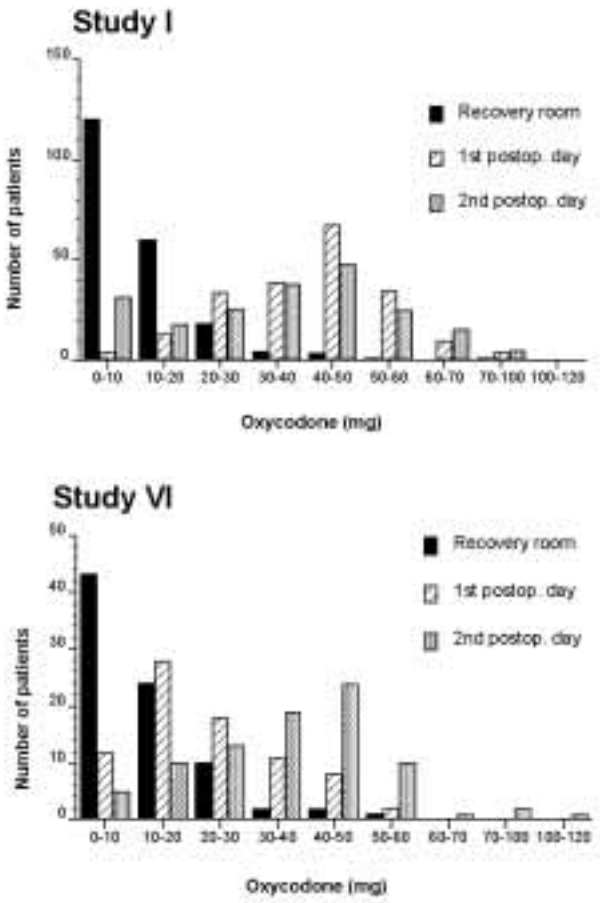


Table 15: Opioids given in studies I and VI

	All patients	*Patients with persistent postthoracotomy pain*	*Patients without persistent postthoracotomy pain*
Study I	N = 207	N = 59	N = 75
Median dose of oxycodone (mg) (range) given			
In the recovery room	9 (0–88)	9 (0–44)	8 (0–50)
1st postoperative day	40 (0–90)	40 (12–80)	40 (7–90)
2nd postoperative day	32 (0–70)	36 (0–70)	36 (0–70)
Cumulative first 2 days	81 (10–188)	86 (12–145)	84 (10–140)
Study VI	N = 63	N = 17	N = 46
Median dose (mg) (range) of opioids given			
In the recovery room	7 (0–52)	10 (0–52)	6.5 (0–27)
1st postoperative day	16 (0–70)	14 (0–70)	17 (0–58)
2nd postoperative day	36 (0–118)	40 (0–118)	35.5 (0–62)
Cumulative first 2 days	62 (7–170)	79 (34–170)	61 (7–117)

Table 16: Morphine consumption in thoracotomy studies II and III

	Cumulative amount of morphine during first 44 hours after surgery	
	Median	*Range*
Study II		
Placebo	135.3	35.0 – 238.4
Diclofenac	39.0	10.0 – 105.3
Study III		
Intercostal	104.0	35.6 – 208.6
Epidural	110.0	39.6 – 196.9
Paravertebral	80.9	46.4 – 195.9

In all other studies (studies II – V), the patients were allowed to take supplementary doses of morphine via a PCA device. In study II, consumption of PCA Mo was significantly less in the diclofenac group compared with the control group during both the first 20-h study period (CI_{95} 13.3 – 34.2; mean 23.7 mg vs. 45.5 – 86.4; mean 66.0 mg; $p = 0.002$) and the first 44-h study period (CI_{95} 28.5 – 62.9; mean 45.7 mg vs. 95.8 – 157.2; mean 126.5 mg; $p = 0.0001$). Three patients in the diclofenac group and nine patients in the control group required i.m. Mo injections to supplement PCA Mo. The consumption of morphine decreased significantly from the first to the second postoperative day in the diclofenac group ($p < 0.05$), but not in the control group. In study III, there were no significant differences in morphine consumption between the groups (epidural, paravertebral, and intercostal) (Table 16).

In study IV, the cumulative consumption of PCA Mo was significantly less in the diclofenac and ketorolac groups compared with the placebo group from 16 h to 44 h after surgery ($p < 0.05$). The 95% confidence intervals (CI_{95}) for cumulative morphine consumption 20 h after surgery were 33.2 – 81.7 (mean 57.4 mg) in the placebo group, 11.9 – 30.0 (mean 21.0 mg) in the diclofenac group and 8.4 – 54.8 (mean 31.6 mg) in the ketorolac group. The CI_{95}s for cumulative morphine consumption 44 h after the operation were 54.3 – 129.1 (mean 91.7 mg) in the placebo group, 16.4 – 53.5 (mean 34.9 mg) in the diclofenac group and 10.9 – 76.3 (mean 43.6 mg) in the ketorolac group.

In study V, the PCA Mo group required significantly more i.v. Mo than the i.t. Mo group ($p < 0.05$) during the first 12 postoperative hours. At 12 h the mean cumulative morphine consumption in the PCA Mo group was 30 mg (range 6 – 112.6 mg, median 24.6) compared with a mean of 10 mg (range 0 – 30.2 mg, median 8.4) ($p < 0.05$) in the i.t. Mo group. The 95% confidence intervals (CI_{95}) for cumulative morphine consumption 20-h after the operation were 15.4 – 74.4 (mean 44.9 mg) in the PCA Mo group and 11.7 – 31.7 (mean 21.7 mg) in the i.t. Mo group. The CI_{95}s for cumulative morphine consumption 44-h after the operation were 23.4 – 113.4 (mean 68.4 mg) in the PCA Mo group and 25.1 – 61.0 (mean 43.0 mg) in the i.t. Mo group. The duration of analgesia in the i.t. Mo group, determined as the time elapsed from induction to the first supplemental PCA morphine dose, was on average 6 hours (range 2 – 22 hours).

Cumulative morphine consumption in patients treated with diclofenac for postoperative pain after thoracotomy and thoracoscopy in studies II and IV was comparable (Figure 7). In all studies the lowest consumption of morphine was detected in patients treated with NSAIDs (i.e. diclofenac or ketorolac) (Figure 8). The mean differences in consumption of morphine in studies II – IV are presented in Table 17.

Figure 7: Consumption of morphine in patients given diclofenac (studies II and IV)

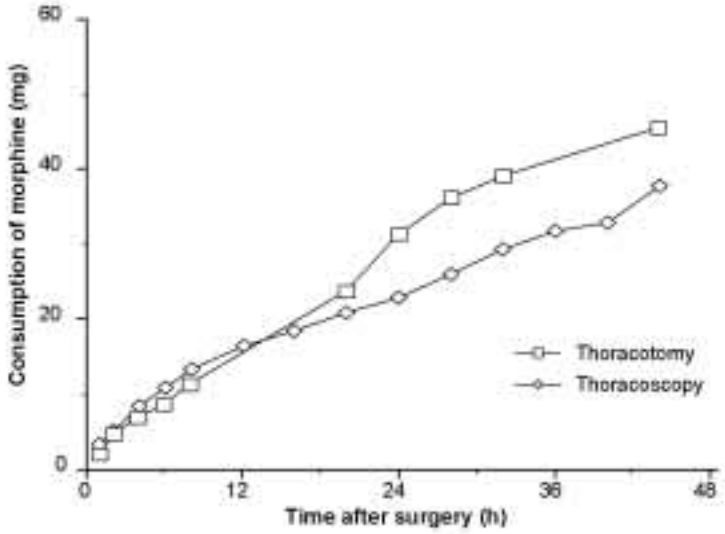


Figure 8: Consumption of morphine in all interventional groups (studies II – V)

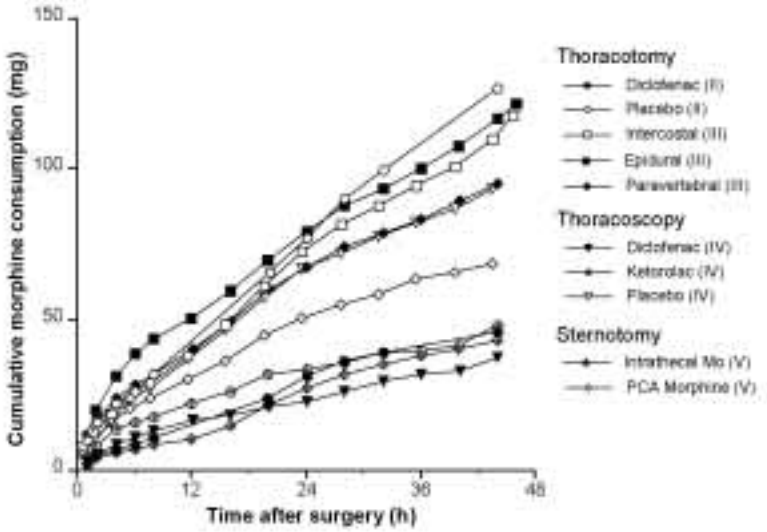


Table 17: Mean differences in consumption of morphine in studies II – IV

	Mean difference	95% Lower	95% Upper	P
Study III intercostal vs. study II diclofenac	64.0	31.6	96.5	0.0003
Study III intercostal vs. study IV diclofenac	72.0	33.5	110.6	0.0004
Study III intercostal vs. study IV ketorolac	61.6	18.1	105.0	0.0021
Study III epidural vs. study II diclofenac	70.6	37.6	103.6	< 0.0001
Study III epidural vs. study IV diclofenac	78.6	39.3	117.9	0.0001
Study III epidural vs. study IV ketorolac	68.1	24.0	112.2	0.0007
Study III paravertebral vs. study II diclofenac	49.5	22.3	76.8	0.0055
Study III paravertebral vs. study IV diclofenac	57.5	26.3	88.7	0.0044
Study III paravertebral vs. study IV ketorolac	47.1	9.6	84.6	0.019
Study II diclofenac vs. study II placebo	–80.8	–115.0	–46.6	< 0.0001
Study II diclofenac vs. study IV placebo	–47.5	–84.0	–11.0	0.0222
Study II placebo vs. study IV diclofenac	88.8	47.8	129.7	< 0.0001
Study II placebo vs. study IV ketorolac	78.3	32.7	123.9	0.0001
Study IV diclofenac vs. study IV placebo	–55.5	–97.8	–13.2	0.0151

8.3 Safety variables

8.3.1 Respiratory status

In study II arterial oxygenation was significantly greater in the diclofenac group compared with the placebo group at 4, 6 and 20 hours with oxygen supplementation and at 20.5 h without oxygen supplementation. There were no significant differences in the actual $PaCO_2$ values between the groups, but the mean increase in $PaCO_2$ from the preoperative values to those at 20 h was significantly greater ($P < 0.05$) in the placebo group (20 (3.3)%) compared with the diclofenac group (7.5 (4.1)%). No atelectasis was seen in any of the postoperative chest x-rays.

In study III, there were no significant differences between the groups in respiratory rate, arterial oxygen tension (PaO_2), SpO_2 or the percentage change in FEV_1 from the preoperative value. In study IV, the groups were comparable with regard to changes in FVC and FEV_1. There were no significant differences in PaO_2 or $PaCO_2$ values between the groups.

In study V the FVC values, when compared with the baseline values, recovered better in the i.t. Mo group than in the PCA Mo group during the first 24 hours ($p < 0.05$). FVC% was 60 ± 8% at 8h in the i.t. Mo group while the corresponding value in the PCA Mo group was 33 ± 5.2% ($p < 0.05$). FEV_1 was less suppressed when compared with the baseline measurements in the i.t. Mo group than in the PCA Mo group at 6, 20 and 24h ($p < 0.05$). FEV_1% at 6 h was

62.2 ± 7.3% in the i.t. Mo group compared with 37 ± 4% ($p < 0.05$) in the PCA Mo group (Figure 9).

The decrease in FEV_1 after different types of operations, i.e. thoracotomy, thoracoscopy and sternotomy, is presented in Figure 10.

Figure 9: Change in FEV1% in the i.t. Mo and the PCA Mo groups (study V)

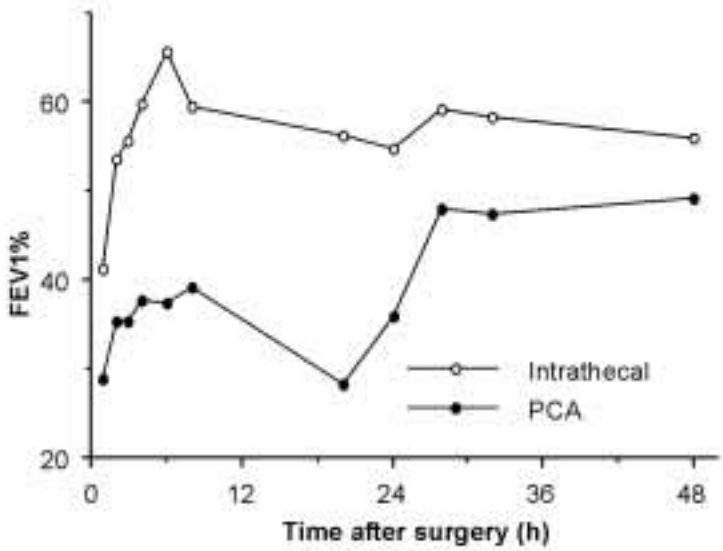


Figure 10: Decrease in FEV_1 after different types of operations (control patients)

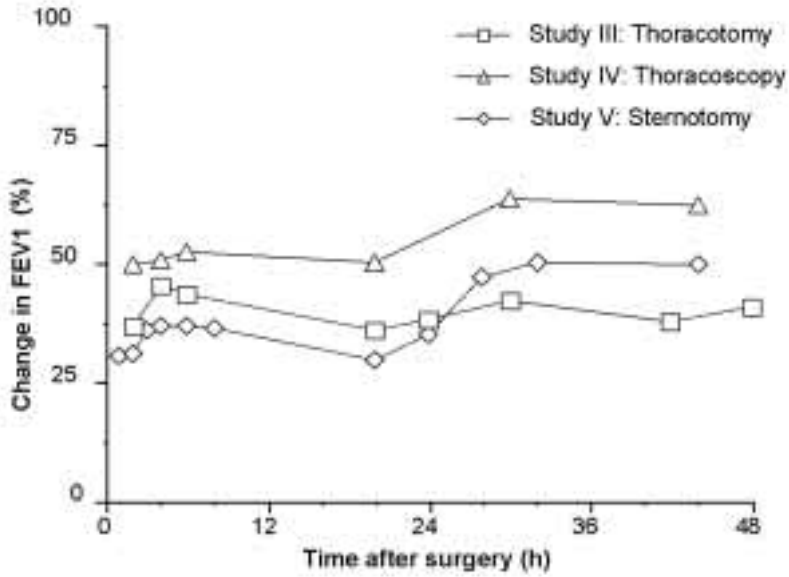


Table 18: Diuresis in studies II – IV

	Urine output (ml) 1. postoperative day	*Urine output (ml) 2. postoperative day*	*Crystalloid solutions given (ml/kg) 1st day after operation*
Study II			
Diclofenac	41 [0–400]	1220 [700–2200]	33 (2)
Placebo	230 [0–850]	1268 [350–2050]	35 (2)
Study III			
Intercostal	565 [50–1050]	1211 [600–2700]	N.A.
Epidural	574 [125–1300]	1280 [800–2150]	N.A.
Paravertebral	601 [100–1040]	1296 [350–2100]	N.A.
Study IV			
Diclofenac	653 [30–1700]	1645 [700–3150]	41 (1.8)
Ketorolac	508 [50–1300]	2331 [1100–3450]	41 (0.8)
Placebo	772 [100–1600]	2224 [1300–3300]	37 (1.3)

N.A. = not available

8.3.2 Urine output and kidney function

In study II there were no statistically significant differences in the creatinine-values between the groups either pre- or postoperatively. Urine output was significantly lower in both groups on the first postoperative day than on the second postoperative day ($p < 0.01$). Urine output during the first postoperative day was significantly lower ($p < 0.05$) in the diclofenac than in the control group. There were no significant differences in the amounts of crystalloids infused between the two groups.

In studies III and IV there were no statistically significant differences in the creatinine values, in the urine output during the first and second postoperative days, or in the amounts of crystalloids infused between the different groups (Table 18).

8.3.3 Haematological variables

The prestudy values for the platelet adhesion test, Ivy bleeding time, platelet count and thromboelastography variables were comparable in the different groups in studies II and IV and did not differ significantly between or within the groups at the various time points, with the exception of the platelet count, which decreased with time in study II in both groups (Table 19, Table 20, and Table 21).

Table 19: Blood loss in studies II – IV

Mean [range]	Peroper	Day 1	Day 2
II Diclofenac	423 [100 – 1300]	480 [100 – 850]	351 [0 – 650]
II Placebo	570 [0 – 2700]	535 [110 – 1900]	365 [50 – 900]
III Intercostal	168 [0 – 400]	487 [200 – 1760]	323 [50 – 1000]
III Epidural	283 [0 – 1200]	463 [160 – 1100]	338 [20 – 900]
III Paravertebral	163 [0 – 650]	415 [130 – 700]	299 [20 – 520]
IV Diclofenac	7.5 [0 – 50]	116 [0 – 200]	–
IV Ketorolac	20 [0 – 100]	123 [20 – 350]	–
IV Placebo	20 [0 – 150]	139 [25 – 300]	–

Table 20: Adeplat (%) in studies II and IV

Mean (SD)	Preop.	2 h	24 h
II Diclofenac	99.2 (1.3)	99.5 (0.6)	–
II Placebo	98.7 (2.3)	98.5 (2.4)	–
IV Diclofenac	96.2 (5.0)	91.6 (21.2)	95.1 (6.5)
IV Ketorolac	94.8 (5.4)	95.1 (4.3)	95.0 (2.4)
IV Placebo	91.8 (7.6)	95.1 (5.0)	96.8 (3.7)

Table 21: IVY bleeding time (min) in studies II and IV

Mean (SD)	Preop.	2 h	24 h	48 h	72 h
II Diclofenac	6.0 (2.3)	5.7 (1.2)	6.4 (2.1)	6.0 (2.5)	5.4 (2.2)
II Placebo	5.5 (1.2)	5.3 (1.9)	5.4 (1.8)	5.1 (1.7)	5.2 (1.7)
IV Diclofenac	6.3 (1.9)	5.2 (1.7)	6.2 (1.9)	–	–
IV Ketorolac	5.6 (2.4)	6.1 (2.1)	6.7 (2.0)	–	–
IV Placebo	5.7 (1.2)	5.7 (1.2)	4.8 (1.5)	–	–

8.3.4 Plasma drug concentrations

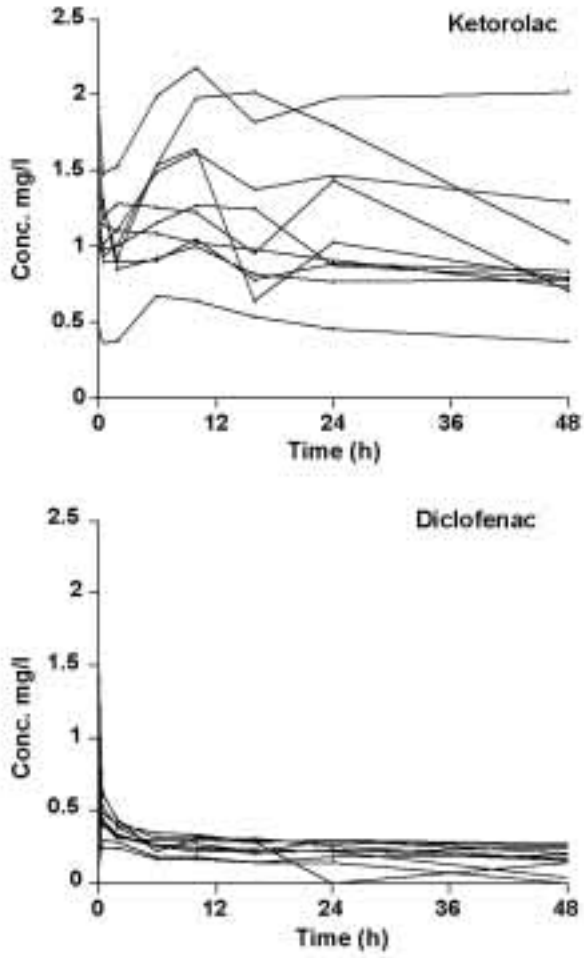
8.3.4.1 Bupivacaine

In study III the plasma concentrations of bupivacaine differed significantly between the groups. Up to 2 hours after the block, bupivacaine concentrations were higher in the intercostal group than in the epidural or paravertebral group. Bupivacaine concentrations were significantly lower in the intercostal group than in the two other groups from 6 h after the block. There appeared to be a wider range in the bupivacaine concentration in the paravertebral group than in the other two groups (range at 48 h: paravertebral 0.45 – 5.1 µg/ml vs. epidural 0.38 – 1.88 µg/ml; range at 10 min: intercostal 0.19 – 1.46 µg/ml).

8.3.4.2 NSAIDs

The individual plasma concentration curves for diclofenac and ketorolac in study IV are presented in Figure 11. The interindividual variation in the time-concentration curves was somewhat greater in the ketorolac group than in the diclofenac group.

Figure 11: Individual plasma concentrations of NSAIDs in study V



8.3.4.3 Morphine

In study V the plasma concentrations of morphine differed significantly between the groups up to 4 h postoperatively. At this time they were 7.2 ± 4.2 ng/ml in the i.t. Mo group vs. 18.8 ± 3.9 ng/ml in the PCA Mo group ($p < 0.03$).

8.4 Adverse events of analgesic therapy

There were no significant differences in adverse events between the groups in studies II – IV. In study V the incidence of adverse events was comparable in both groups, except that on the first postoperative day nausea combined with headache ($p < 0.05$) and itching ($p < 0.05$) differed statistically between the groups (Table 22). In study II, 13 patients in the diclofenac group and 9 patients in the control group had a urine output below 100 ml during the first postoperative day, but no significant difference could be detected between the groups (Table 18).

In study III 4 patients in the epidural group, 3 in the paravertebral group and one patient in the intercostal group had serious respiratory depression ($PaCO_2 > 8$ kPa = 60 mmHg) more than 2 h after surgery. Six patients (2 in the intercostal group, 3 in the paravertebral group and one in the epidural group) had moderate respiratory depression ($PaCO_2$ 7 – 8 kPa = 52 – 60 mmHg). Six of these 14 patients were obese and 2 of them had a history of hypertension. Nine of these patients had consumed 1.5 – 2 times the mean dose of morphine. In four of the patients there was no obvious explanation for the respiratory depression.

In study V $PaCO_2$ was slightly elevated in both groups. The samples for blood gas analysis were taken with the patients at rest. When the individual patients were analysed, at 2 h moderate respiratory depression ($PaCO_2$ 7 – 8 kPa) was seen in 4 patients in the i.t. Mo group. All these 4 patients in the i.t. Mo group had needed supplementation with i.v. PCA morphine during the first 2 hours already. Two cases of serious respiratory depression ($PaCO_2 > 8$ kPa) were observed in the i.t. Mo group at 4 and 5 h. One patient in the i.t. Mo group required naloxone for respiratory depression.

Table 22: Adverse events in studies II – V

	Drowsines		*Confusion*		*Nausea*		*Vomiting*		*Itchning*		*Abdominal pain*		*Dizziness*		*Hallucination*		*Difficulty with breathing*		*Allergic reaction*		*Respiratory depression*		*Urinary retention*		*Headache*		*Nausea combined with headache*		*Sedation*	
Day	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Study II																														
Diclofenac	12	8	2	0	6	2	2	1	3	1	1	0	7	3	1	1	1	1	0	0	0	0	13	0	–	–	–	–	–	–
Placebo	14	10	2	1	6	4	2	1	2	3	0	1	6	5	0	1	2	2	0	0	0	0	9	0	–	–	–	–	–	–
Study III																														
Inter	14	9	2	1	9	4	2	1	3	2	0	0	4	1	0	0	1	1	0	0	3	0	0	0	–	–	–	–	–	–
Epid	14	13	1	6	5	2	0	0	2	7	0	0	6	3	1	1	4	4	0	0	5	0	0	0	–	–	–	–	–	–
Para	13	12	2	2	3	1	0	1	4	3	0	0	1	2	0	0	1	1	0	0	6	0	0	0	–	–	–	–	–	–
Study IV																														
Diclofenac	5	3	2	0	2	1	0	0	4	0	0	0	0	1	0	1	0	0	0	0	0	0	–	–	–	–	–	–	–	–
Ketorolac	7	4	0	0	2	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	–	–	–	–	–	–	–	–
Placebo	8	6	0	1	2	1	1	2	1	1	0	0	0	0	0	0	0	2	0	0	0	0	–	–	–	–	–	–	–	–
Study V																														
Intathecal	–	–	–	–	2	1	–	–	2	4	–	–	–	–	–	–	–	–	–	–	4	0	6	1	0	0	0	4	10	0
PCA–Mo	–	–	–	–	1	0	–	–	0	0	–	–	–	–	–	–	–	–	–	–	0	0	2	0	0	1	0	0	7	0

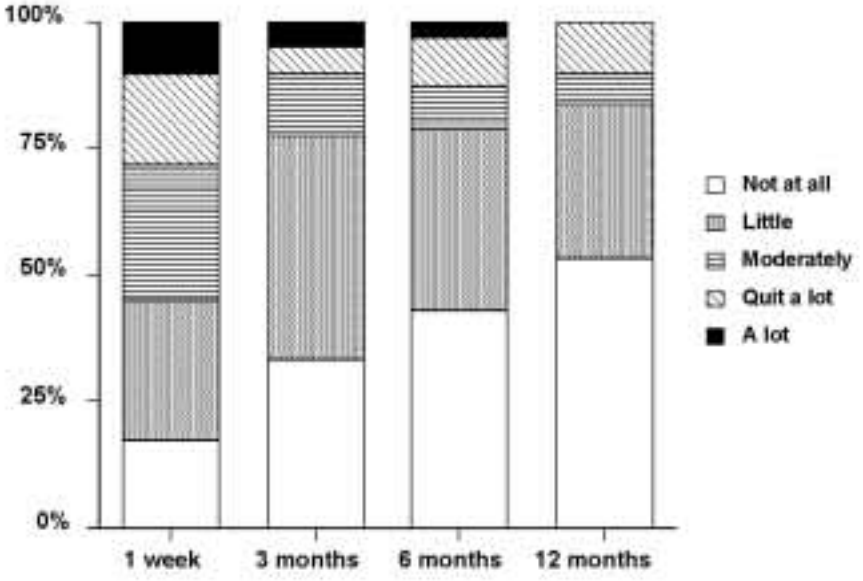
8.5 Chronic pain after thoracotomy

8.5.1 Incidence of chronic postthoracotomy pain

In study I the incidence of persistent postthoracotomy pain was 44% (n = 134) with a mean follow-up time of 30 months (15 – 48 months). In this study there was no statistically significant difference between the patients who still had pain and those who were free of pain with regard to patient characteristics or the pain treatment received during the two first postoperative days.

In study VI persistent postthoracotomy pain interfered with normal daily life in more than 50% of the patients (Figure 12). Sleep disturbances were reported by 25% – 30% of the patients. Among the major factors aggravating the pain the patients reported carrying heavy objects, changes in the weather, walking around, lying on the operated side, sitting, feeling depressed and working with the hand of the operated side. Most patients experienced chronic postoperative pain around the scar. The pain was described as aching pain and/or tenderness by half of the patients and as numbness by one fourth of the patients.

Figure 12: Limitation in daily life in study VI



8.5.2 Severity and duration of chronic pain after thoracotomy (Studies I and VI)

In study I, there was a statistically significant correlation between the nurses' reports on pain and the amount of opioids the patients received during the 1st and 2nd postoperative day and the amount of non-steroidal anti-inflammatory drugs (NSAIDs) given during the 1st postoperative day.

In study VI the incidence of chronic pain was similar in patients with malignant and benign disease. Interestingly, the patients who had persistent postoperative pain 6 months after surgery had consumed significantly more analgesics during the immediate postoperative period compared with the patients without persistent pain. However, there was no significant difference in the reported intensity of pain one week after surgery between patients with or without chronic pain at 6 months.

In study I, the pain experienced during the first postoperative week was rated as minor by 60% of the patients, as considerable by 35% and as excruciating by 5%. The obtained pain relief was considered good in 60%, satisfactory in 38% and poor in 2% of the answers. Interestingly, the patients who had chronic postthoracotomy pain at the time of the interview had experienced significantly more pain immediately after surgery than the patients who had no chronic pain. There was a significant correlation between severity of pain experience and poor efficacy of pain relief, i.e. patients who had experienced more pain also rated their pain relief as poorer. There was no statistically significant correlation between the patients' experience of the severity of pain and the amount of either opioids or NSAIDs administered. In order to improve postoperative pain relief the patients stated in the interview that they would have wanted additional analgesia as follows: analgesics more frequently (19%) or in higher dosages (4%), local anaesthetic blocks (3%) or NSAIDs (2%).

Chronic postthoracotomy pain was localised in the area surrounding the incision in 82% of the cases in study I and in 90% of the cases in study VI. The pain was described as aching or tender in 30 – 45%, combined with numbness in 25 – 40%. More than one type of pain was reported by 40% of the patients. The pain descriptions suggest an 8% incidence of intercostal neuralgia (numbness with tenderness or burning pain). Treatment consisting mainly of analgesics was received by 66% of the patients in study I.

8.5.3 Predisposing factors

In study VI, more severe chronic pain 3 and 6 months after surgery was associated with higher consumption of NSAIDs during the first five postoperative days ($p = 0.04$ and 0.03, respectively). Patients with no pain or mild pain ($n = 46$) 6 months after surgery had taken on average 3.2 daily doses of NSAIDs during the first 5 postoperative days while patients with moderate, severe or excruciating pain ($n = 17$) had taken 4.4 daily doses of NSAIDs ($p = 0.03$). Patients who had no pain or mild pain ($n = 46$) 3 months after surgery had been given a mean of 62.8 mg (range 7 – 117 mg) opioids expressed as equianalgesic doses of morphine during the first two postoperative days and patients having moderate, severe or excruciating pain ($n = 17$) had received 78.9 mg (range 34 – 170 mg) opioids ($p = 0.06$).

9 DISCUSSION

9.1 Methodological aspects

9.1.1 Assessment of analgesia

In study II the PCA device was used as a tool to assess analgesia. The morphine bolus dose was always the same, i.e. 3 mg followed by a tail dose of 2 mg given over 60 min, and the dose was not adjusted according the patient's weight. Prestudy pain scores could only be obtained for two of the patients in each group, as patients were generally unable to co-operate when arriving in the recovery room due to residual anaesthesic effects. In the immediate postoperative period the conventional 10-cm visual analogue scale is generally difficult to use as the patient's psychomotor skills have not yet recovered after emergence from general anesthesia. A 50-cm visual analogue scale was therefore used to assess the postoperative pain in place of the conventional scale (Tigerstedt and Tammisto 1988). In study V postoperative pain was measured only by VAS at rest. In studies II – IV pain was assessed at rest, when moving and when coughing. This is important, as pain intensities are significantly higher e.g. when coughing compared with at rest.

In study III, the patients in the three groups titrated themselves to comparable levels of analgesia (Ferrante et al. 1988). Thus, in this situation, the consumption of PCA morphine can be considered a valid measure of the efficacy of the various local anaesthetic blocks. One hour after surgery pain at rest was surprisingly high in all three groups in study III. The time interval between injection of bupivacaine and assessment of the patients' blocks in the PACU was approximately one hour, which should have been sufficient for development of the skin analgesia associated with the three techniques (intercostal, epidural or paravertebral). Using peroperative opioids might have produced superior pain relief in the immediate postoperative period but such an approach might have obscured the potential differences in the analgesic efficacy of the three different local anaesthetic blocks. A recent study has suggested certain predictive factors of early morphine requirements. These include certain ethnic groups, emergency surgery, major surgery, surgery exceeding 100 min, pain score on arrival in PACU, and intraoperative opioid dose (Dahmani et al. 2001).

9.1.2 Sample size and study design

It could be argued that the numbers of patients in studies III and IV were too small to reveal any significant difference between the groups in the main parameter i.e. consumption of morphine. However, in study II a significant difference between the groups, which received an intrathoracic intercostal nerve block with and without intravenous infusion of diclofenac, was detected with similarly sized patient groups using consumption of PCA morphine as the main indicator of analgesic efficacy. A power calculation suggests that 114 patients in each treatment group would have been required in study III to detect a difference of 20% in the consumption of morphine. Likewise, in study IV, with an α-error of 0.05 and β-error of 0.20 the power analysis indicated that ten patients would have been required per group to detect a 75 mg difference in the consumption of morphine between the diclofenac and the placebo groups during a 48-hour period. A standard deviation of 58.6 (placebo) and a mean difference between the groups of 93 mg in 48 hours was used in this calculation. Moreover, the sample size calculation was based on study II that had a similar study design. The difference between the placebo and diclofenac treatments in study IV, however, was 57 mg during the first 44 hours. The small size of the patient groups in study V was due to the rareness of myasthenia gravis.

9.1.3 Ethical aspects

The Institutional Ethics Committees approved all study protocols. Two of the consecutive studies (III and V) were not placebo-controlled as ethical reasons prohibited double-blinding and placebo-controlling in these studies. I.v. morphine with PCA device was used as rescue medication in all consecutive studies. The fact that ten patients in the control group required additional i.m. doses of morphine indicates that excess caution may have been exercised in study II when programming the PCA-device (Ferrante et al. 1988, Sudarshan et al. 1995). The lock out time of 30 min was probably too long. A better choice may have been to abandon the tail dose and use a shorter lock out time and a 1-hour maximum dose limit (Silvasti et al. 1998).

9.1.4 Model of stress

Diclofenac 75 mg i.m. and ketorolac 30 mg i.m. have demonstrated equal efficacy in pain reduction and opioid requirement both after laparoscopy (O'Hanlon et al. 1996) and after maxillofacial surgery (Tarkkila et al. 1996). While a significant morphine sparing effect after thoracoscopic surgery through use of both diclofenac and ketorolac was detected in study IV, no significant difference could be found between the two NSAIDs in this regard. One explanation for this might, of course, be that the type of surgery, i.e., thoracoscopy, caused less pain than had been predicted when the study was started. Confidence intervals of 95% for cumulative morphine consumption suggest some difference between the diclofenac and ketorolac groups, though a statistically significant distinction could not be detected due to the small numbers of patients in each group.

9.1.5 Assessment of respiratory function

One of the hypotheses studied was that unilateral analgesia with a paravertebral or intercostal block on the side of the surgical incision and wound would provide similar analgesia to an epidural block but with better preserved respiratory function. The advantage of a unilateral block concerning respiratory function could not be shown in study III. However, the spirometry values were slightly less reduced after paravertebral blocks than in the other two groups. The difference was not statistically significant. This finding is in line with the similar opioid consumption and comparable VAS values at rest in all three groups in study III.

Due to significant variations in the definition of respiratory depression between different studies it was not possible to compare the frequency of this symptom in the studies conducted and the reference studies used. In some studies respiratory depression is defined as need for naloxone while in others it is defined as a decline in respiratory rate and increase in CO_2. Nevertheless, in study V the spirometry values after sternotomy can be interpreted as a dynamic measurement in which postoperative pain plays a major role.

9.1.6 Haematological variables

When evaluating the effects of NSAIDs on thrombocyte function no significant conclusions can be drawn from the platelet counts alone. The platelet counts are affected by bleeding and volume replacement, and should thus at least be adjusted by the haematocrit. The quality of information on any effects of the NSAIDs on platelet function can be improved by using the platelet adhesion test which measures the proportion of functional thrombocytes. As a qualitative measure of viscoelastic clot strength, thromboelastography examines the entire blood coagulation (Mallett and Cox 1992).

Thus, this test can be used to assess the interaction of the protein coagulation cascade, fibrinogen, and the platelet surface as a unit.

9.2 Analgesic efficacy

9.2.1 Diclofenac and ketorolac

While not in the domain of this thesis, it is worth mentioning that in orthopaedic surgery both diclofenac (Lindgren and Djupsjö 1985) and ketorolac have previously been shown to be effective in pain alleviation. Both diclofenac and ketorolac have also been shown to be equally effective in reducing pain and opioid requirements after laparoscopy (O'Hanlon et al. 1996), after maxillofacial surgery (Tarkkila et al. 1996), and after major surgery i.e. orthopaedic, abdominal, gynaecological, urological, cardiac and thoracic surgery (Forrest et al. 2002). As is widely known, however, the results have been more varied after abdominal surgery (Hodsman et al. 1987, Tigerstedt et al. 1987). A previous study (Rhodes et al. 1992) has shown diclofenac 75 mg i.m. twice daily to have a significant morphine sparing effect after thoracotomies. Similarly, ketorolac has been shown to be effective in postthoracotomy pain treatment (Power et al. 1994, Carretta et al. 1996, Singh et al. 1997).

In study II, the diclofenac group showed a notably lower morphine consumption compared with the placebo group during both the first and the second 24-h study periods. In the immediate postoperative period up to 2 h, the VAS values were significantly lower ($P < 0.05$) in the diclofenac group, in which the patients were given a bolus dose of the study drug over the first 15 minutes after arrival in the PACU.

There was notably lower average consumption of morphine by the diclofenac group in study II during the second postoperative day (only 14 mg or less than 25% of the dose required by the control group). This effect is quite plainly demonstrated by the decrease in the steepness of the slope of the morphine consumption curve after the first 24 hours in the diclofenac group which is not present in the placebo group. The alleviating effect of NSAIDs on inflammation at the wound site on the second postoperative day (Mather 1992, Moote 1992) may be one factor explaining the reduction in experienced pain. Alternatively, or additionally, this could be the result of acute tolerance to morphine at higher doses (McQuay et al. 1981).

In patients undergoing major thoracic surgery administration of lysine acetyl salicylate 1.8 g 6-hourly has been shown to provide postoperative pain relief similar to that derived from infusion of morphine 10 mg every six hours (Jones et al. 1985). In contrast to a study by Pavy et al (Pavy et al. 1990) in which administration of indomethacin suppositories (200 mg daily) after thoracic surgery resulted in a 30% decline in papaveretum consumption over 48 h, study II demonstrated a clinically significant reduction of 67% in morphine consumption. One explanation for the smaller opioid sparing effect of indomethacin in the study by Pavy and co-workers as compared with the results of study II might be that the control patients in their study did not receive enough papaveretum. This hypothesis is supported by the fact that the patients treated with indomethacin had not only significantly less pain at all evaluation times (Pavy et al. 1990), but also considerably less pain after physiotherapy than the patients in the control group. Admittedly, other factors such as the different NSAIDs used and the different administration techniques may also have played a role. The substantial difference between the two study outcomes does, however, imply that the design of the control group and the administration procedures may have a significant impact on the clarity of the study outcome and should therefore be given just as much attention as the test group design.

Surprisingly, although VATS is considered a less traumatic procedure compared with conventional thoracotomy (Landreneau

et al. 1993) patients appear to experience moderate or even severe pain immediately after the procedure. Supporting these findings, Kirby and co-workers (Kirby et al. 1995), while observing significantly more postoperative complications in the thoracotomy group compared with VATS, found no difference in postoperative pain between the groups.

In study IV all operations were minor thoracic procedures, i.e. biopsies of the lung or of the pleura, sympathectomies or extirpations of small benign tumours. In line with the findings of Landreneau and Kirby, the small difference in pain experience was also made evident by the mean cumulative consumption of morphine during the first postoperative day in this study which was only 17% less in the VATS placebo group than after thoracotomies in a similarly designed study (study II). Correspondingly, in the VATS diclofenac group consumption of morphine was 30% less than after thoracotomies in diclofenac group. The fact that the patients in study II had received intercostal blocks with 0.5% bupivacaine might explain the small difference between studies IV and II. These various findings would imply that, putting aside the clearly important difference in the level of postoperative complications, if the patients' comfort is a significant consideration, pain treatment is equally imperative in both VATS and thoracotomies irrespective of the apparent degree of trauma.

No statistically significant difference in the morphine sparing effects of the two NSAIDs was shown in study IV, probably due to the small sample size. While the 95% confidence intervals for cumulative morphine consumption indicated a possible difference between the diclofenac and ketorolac groups, this could not be verified due to the small numbers of patients in each group. Despite the fact that no difference was detected between the two NSAIDs in this regard, both were shown to have a significant morphine sparing effect after thoracoscopic surgery when compared to placebo.

9.2.2 Regional anesthesia

Study III indicates that intercostal blockade produced superior early analgesia compared with continuous epidural and paravertebral blockade. This is supported by the fact that the patients in the intercostal group only experienced significantly less pain when coughing at 2 and 4 h after the operation compared with the epidural group.

While the overall efficacy of the three regional anaesthetic methods examined in study III was not particularly good, the practically equal effectiveness of the intercostal block and the two continuous blocks was unexpected even though one-third of the patients in a recent study had problems with the epidural technique (McLeod et al. 2001). Satisfactory pain relief was achieved in two-thirds of the patients but one patient in five experienced poor pain relief. The fact that the intercostal block was just as good as the two continuous blocks may be explained by the intercostal block causing a prolonged though small reduction in pain perception. Furthermore, the relative ineffectiveness of the two continuous blocks in study III might be attributable to the relatively moderate dose of bupivacaine (Dollery 1999c). The study design prescribed a 0.25% solution of bupivacaine and deliberately avoided exceeding the recommended daily dose of bupivacaine (400 mg) (Martindale 2002). Hence, the infusion volume of bupivacaine used in the study may have been insufficient.

The relative ineffectiveness of the two continuous blocks in study III might also be explained by the phenomenon of disaggregation (Conacher 2001). Continuous epidural and paravertebral blocks with local anaesthetics do not prevent ipsilateral shoulder pain as a result of phrenic nerve mediated nociception of diaphragmatic irritation. Burgess and co-workers demonstrated shoulder pain in 86% of patients undergoing either lobectomy or pneumectomy despite continuous epidural analgesia with fentanyl alone or with a combination of fen-

tanyl and bupivacaine and concluded that there was a close relationship between the shoulder pain and the transection of a major bronchus (Burgess et al. 1993). Unfortunately, study III did specifically address shoulder pain. Addition of a suprascapular nerve block did not relieve ipsilateral shoulder pain after thoracotomy in patients receiving thoracic epidural analgesia with a combination of bupivacaine and fentanyl (Tan et al. 2002). Curiously though, interscalenic brachial plexus blockade with lignocaine or with bupivacaine (Ng and Chow 1997) as well as blockade of the phrenic nerve with lignocaine (Scawn et al. 2001) have been shown to be effective in treatment of ipsilateral shoulder pain after thoracotomy in patients with continuous thoracic epidural blockade for treatment of postoperative pain. Still, one should keep in mind that interscalenic brachial plexus blockade and phrenic nerve blockade carry a risk of diaphragmatic paresis that can impair the cough mechanism and result in atelectasis in the presence of intercostal motor weakness caused by thoracic epidural block.

Previous studies (Kaplan et al. 1975, Faust and Nauss 1976, Toledo-Pereyra and DeMeester 1979) have advocated the use of intrathoracic intercostal nerve blocks as a reliable method for immediate postoperative pain relief as they are easy to perform during the operation. Sabanathan and co-workers (Sabanathan et al. 1988, Sabanathan et al. 1990) have supported these recommendations by showing that continuous paravertebral blockade with bupivacaine provided significantly superior pain relief and pulmonary function after thoracotomy compared with placebo. Using the same method as Sabanathan and co-workers to perform continuous paravertebral blockade, Richardson and co-workers demonstrated the combination of continuous paravertebral block, NSAID and systemic opioid to be the most effective pain treatment method after thoracotomy (Richardson et al. 1994, Richardson et al. 1999). Owing to the differences in methodology the findings in study III are difficult to compare with the results of Sabanathan and co-workers and Richardson and co-workers. In study III, pain was treated with blocks using only local anaesthetic solutions combined with i.v. PCA morphine whereas Richardson and co-workers additionally used diclofenac 50 mg 8-hourly orally or rectally (Richardson et al. 1999). Furthermore, in study III the dose of bupivacaine was exactly the same in the paravertebral and epidural groups whereas Richardson and co-workers used double the amount of local anaesthetic solution in the paravertebral group compared with the epidural group. Regrettably, the only study (Matthews and Govenden 1989) with results resembling those of study III with epidural and paravertebral local anaesthetic blocks providing equally good postoperative analgesia after thoracotomy, made no mention of use of supplementary analgesics.

9.2.3 Intrathecal morphine

When residual anaesthesia and incisional pain are combined with the diminished pulmonary reserves patients with myasthenia gravis are particularly vulnerable to respiratory complications during the postoperative period (Drachman 1994). With the aim of optimising the immediate recovery phase, study V was designed to utilise i.t. Mo for poststernotomy pain relief. This choice was further influenced by the assumption that i.t. opioid analgesia is considered predictable, technically easy and reliable (Jahr and Bjerke 1991). Disadvantages of i.t. opioid analgesia include e.g., nausea, itching, and respiratory depression (Stoelting 1989). With respect to the technical performance i.t. administration may also be regarded as superior to the epidural route (Jahr and Bjerke 1991). The results of study V supported earlier reports that the peak effect of i.t. Mo occurs at 4 to 7 hours (Bailey et al. 1993).

Study V appears to be the first study evaluating the efficacy and respiratory effects of i.t. Mo in myasthenia gravis patients who were extubated immediately after sur-

gery. PCA morphine consumption and VAS scores were used to assess analgesia in study V. In this study the analgesia was equally effective with i.t. Mo and i.v. PCA Mo.

The findings of study V are in line with the hypothesis that the mechanism of the analgesic action of i.t. Mo is mainly spinal (Cousins and Mather 1984, Carr and Cousins 1998). As anticipated, lower plasma morphine levels were seen in the i.t. Mo group during the immediate postoperative period up to the first four hours. Also, pain control was equally good in both groups during this time period with lower i.v. morphine consumption in the PCA Mo group than in the i.t. Mo group. In this study plasma concentrations of morphine were measured for additional clinical information only.

Myasthenia gravis is known for the diversity of its clinical and pathological manifestations and its immunological characteristics (Compston et al. 1980, Drachman 1994). Nilsson and co-workers (Nilsson et al. 1989, Nilsson and Müller 1990) have associated occurrence of the combination of HLA-B8 and anti-AChR-ab with neuromuscular sensitivity to halothane or isoflurane. The elevated anti-AChR-ab titre has also been related to increased vecuronium sensitivity (Nilsson and Meretoja 1990).

Assessed by VAS, study V demonstrated equally good pain relief in the i.t. Mo group and in the i.v. PCA Mo group, although the latter group had a lower total consumption of i.v. Mo. The morphine consumption of the i.v. PCA Mo group is in accordance with a study comparing two different methods for thymectomy, i.e. median sternotomy and thoracoscopic thymectomy, in patients having MG (Rückert et al. 2000). The significantly lower respiratory rate in the i.t. Mo group compared with the i.v. PCA Mo group during the first six postoperative hours might have been due to central respiratory depression or could be an indirect sign of better pain relief in the i.t. Mo group. The occurrence of sporadic respiratory depression suggests that the PCA dose of morphine (30 µg/kg) used in combination with i.t. Mo may have been too high. The i.t. dose of morphine (10 µg/kg) was relatively high compared with the IASP guidelines (Ready and Edwards 1992) and doses used for coronary surgery (0.3 to 0.5 mg) (Heres et al. 1998). Hence, the need for supplemental doses of i.v. PCA Mo among the i.t. Mo patients during the first postoperative hours could be a sign of confusion due to residual anaesthesia or an indirect sign of some form of discomfort other than pain since the VAS values were low.

This conclusion is in agreement with previous observations where the recommended PCA dose was 50% smaller than normally when used concomitantly with i.t. morphine (Gwirtz 1992). The dose of i.v. PCA Mo used in the study was considered safe and justified because the patients were monitored continuously for the first 24 hours.

9.3 Respiratory function

One objective in study II was to explore whether reduced morphine consumption was reflected in improved respiratory function as measured by levels of $PaCO_2$ and PaO_2. Such a phenomenon had been observed in two previous studies where either i.m. ketorolac or i.m. diclofenac was given for pain relief following abdominal surgery in a comparable experimental setting using PCA (Gillies et al. 1987, Hodsman et al. 1987). Indeed, when compared with preoperative values, the increase in arterial $PaCO_2$ was significantly smaller in the diclofenac group in study II. One plausible explanation for the difference in the increase of $PaCO_2$ could be the reduced consumption of morphine in the diclofenac group. Other possible factors explaining the discrepancy in the increase of $PaCO_2$ in study II, such as decreased body temperature or lower metabolic rate, should also be considered (Mortola and Frappell 2000). These factors may also account for the observed beneficial effects of diclofenac infusion on

arterial oxygenation. Support for this concept has been provided by earlier studies indicating that prostaglandin inhibitors may improve peripheral tissue perfusion after coronary artery bypass surgery (Kuttila and Niinikoski 1989).

Based on a previous study comparing postoperative pain and pulmonary function after laparoscopic and open cholecystectomy it could be expected that the type of operation conducted would have an impact on postoperative respiratory function (Hendolin et al. 2000). The lower postoperative FEV_1 values after thoracoscopy and thoracotomy in control patients in studies III and IV support this hypothesis. The method of anaesthesia and postoperative pain treatment has also been shown to have an impact on postoperative respiratory function (Hendolin et al. 1987). Regrettably, it was not possible to compare the impact of different types of anaesthesia as one-lung-ventilation is used for many thoracic operations and thus general anaesthesia is frequently necessary.

It has been suggested that the impact of anaesthesia and surgery on postoperative lung function is related to the diaphragmatic dysfunction that is thought to be secondary to surgical irritation, abdominal distension, and inadequate pain treatment (Miller et al. 1994). In a study by Rückert and co-workers the immediate postoperative lung function declined to 65% after thoracoscopic thymectomy and to 35% after transsternal median thymectomy (Rückert et al. 2000). An earlier study by Cooper et al (Cooper et al. 1978) reported a decrease of up to 50% in vital capacity and peak flow rate in poststernotomy patients with normal muscle strength when parenteral morphine was given for postoperative pain relief. In a cumulative meta-analysis study by Ballantyne and co-workers epidural opioids decreased the incidence of atelectasis compared with systemic opioids, and epidural local anaesthetics increased PaO_2 and decreased the incidence of pulmonary infections and pulmonary complications overall compared with systemic opioids (Ballantyne et al. 1998). The findings of study V are at odds with these earlier conclusions. In this study respiratory function was significantly better restored with i.t. Mo than i.v. PCA Mo. Four hours postoperatively, FVC% in the i.t. Mo group had recovered to 60% and FEV_1% to 57% of the respective baseline values compared with FVC% 32% ($p < 0.05$) and FEV_1% 37% in the PCA Mo group.

9.4 Safety variables

9.4.1 Kidney function

Patients undergoing thoracic operations are often on restricted i.v. fluids to prevent postoperative pulmonary complications. Particularly under increased surgical stress this postoperative fluid restriction can be manifested as reduced urine output in patients receiving NSAIDs for postoperative pain relief (Ellenhorn et al. 1997, Lee et al. 1999). The amount of i.v. fluids was also restricted in study II as the majority of the patients underwent either pneumonectomies or lobectomies. This was manifested particularly in significantly reduced urine output in the diclofenac group even when compared with the admittedly low urine output in the control group. Subsequently, diuresis returned to preoperative values during the second postoperative day and no increases were seen in the plasma creatinine values. In study IV the i.v. crystalloid fluid volumes were comparable with those generally recommended for surgical patients (Kaye and Grogono 2000) and no differences were found between the groups in urine output or serum creatinine values during the first two postoperative days. These findings are in accordance with the results of Fredman and co-workers who investigated the influence of i.v. diclofenac on renal blood flow and glomerular filtration in normovolemic elderly patients undergoing major orthopaedic surgery (Fredman et al. 1995). Treatment with nonsteroidal anti-inflammatory

drugs alone is not considered a significant risk factor for postoperative renal failure (Kim et al. 1999, Rexrode et al. 2001).

9.4.2 Haematological effects

In a previous study Bricker et al. showed no increase in perioperative blood loss during transurethral prostatectomy after oral diclofenac given in a dose of 200 mg in 24 hours (Bricker et al. 1987). Another study (Campbell et al. 1990) demonstrated that 75 mg of i.m. diclofenac increased capillary bleeding time which, however, was unaffected when the same dose was given i.v. The present studies (II and IV) showed no effects of diclofenac or ketorolac on haemostasis as compared with the control group. This concurs with previous findings by Gibbs and Reinhart (Reinhart et al. 1993, Gibbs and Sear 1995). It should be noted, though, that the patients in the two present studies discussed had not had deep venous thrombosis prophylaxis which could potentially increase the risk of haemostatic complications of NSAIDs (Yett et al. 1978, Faunø et al. 1993).

No difference was found between the groups either in the platelet adhesion test or in any of the thromboelastography parameters at two hours from the beginning of the infusion in studies II and IV, and there were no differences in these parameters at 24 hours from the beginning of the infusion in study IV. While Power and co-workers reported that platelet aggregation was significantly decreased one hour after an i.m. injection of 1.2 mg/kg of diclofenac (Power et al. 1990), these results are not directly comparable with the findings of the present studies as in the study by Power and co-workers all patients had been given heparin preoperatively. This difference in the results could also be explained in part by the use of different tests and a lower diclofenac dose (0.4 mg/kg in 2 hours) in the present studies compared with the study of Power and co-workers (1.2 mg/kg i.m.).

9.4.3 Plasma drug concentrations

Previous studies have demonstrated much higher bupivacaine concentrations (mean 4.92 µg/ml, maximum 7.48 µg/ml) during continuous infusion in paravertebral blocks (Berrisford et al. 1993). Toxic effects, such as convulsions, have been reported at venous blood levels of approximately 2 – 4 µg/ml of bupivacaine (Covino 1998) and, at even lower plasma concentrations of bupivacaine, some evidence of central nervous system toxicity has been reported (Denson et al. 1984).

Interestingly, in study III, there was noticeable variation between individual patients in arterial plasma concentrations of bupivacaine. This was particularly evident in the paravertebral group in which the bupivacaine concentrations were elevated in all patients as late as 48 h after the start of the infusion. This unevenness in the bupivacaine plasma concentrations could be due to adsorption from and leakage out of the surgically created compartment and may, as such, be difficult to avoid and thus require careful observation. In the paravertebral and the epidural groups the highest individual concentrations of bupivacaine – 5.1 µg/ml and 1.88 µg/ml, respectively – were observed 48 h after the beginning of bupivacaine infusion while in the intercostal group a peak concentration of 1.46 µg/ml was observed 10 min after injection. Nevertheless, no signs of bupivacaine toxicity were detected in any of these patients under close observation during the first 24 h postoperatively. This might be explained by a placebo-controlled study on the incidence of CNS symptoms and changes after intravenous infusion of bupivacaine and ropivacaine which showed a difference in tolerance between the maximum total plasma concentration and the unbound concentration (Knudsen et al. 1997) due to only unbound drug being available for distribution to the tissues.

In study IV, the patients received a continuous infusion of either diclofenac or

ketorolac for a period of 48 h. As diclofenac and ketorolac have different elimination half-lives (diclofenac 1 – 2 h vs. ketorolac 5 h) (Willis et al. 1979, Brocks and Jamali 1992) the plasma concentrations were also measured for 48 h in order to ensure that a steady state concentration was reached. During this time there was higher interindividual variability in the plasma concentrations in the ketorolac than in the diclofenac group. Plasma concentration–time curves for both diclofenac and ketorolac show clearly that all patients treated with either diclofenac or ketorolac had measurable concentrations of NSAID in the blood circulation. No obvious explanation for these variations was detected. Nevertheless, as with other NSAIDs, clinical efficacy is probably not directly related to the plasma concentrations of diclofenac or ketorolac (Dollery 1999a, Dollery 1999b) and it was, therefore, decided that this did not require further consideration.

According to previous studies (Rowland and Tozer 1995) a steady concentration state may be considered to have been reached in 3.3 half-lives, translating to about 16.5 h for ketorolac and 3.5 – 6.5 h for diclofenac. In a single dose study with healthy volunteers the C_{max} after an i.v. bolus dose of 10 mg ketorolac was 2.39 ± 1.30 µg/ml (mean ± SD). In a study by Jung (Jung et al. 1988) the mean plasma concentration after a ketorolac i.v. bolus dose of 10 mg fell from approximately 1 µg/ml to 0.1 µg/ml in 10 h. In another study the mean plasma concentration of diclofenac after an i.v. bolus dose of 50 mg fell from approximately 8 µg/ml to 0.5 µg/ml in 1 h (Willis et al. 1979). Hence, it was expected that due to the administration of a bolus dose of 10 mg ketorolac the time to reach the concentration plateau would be shorter than 16.5 h in study IV and, accordingly, the concentrations of ketorolac and diclofenac reached a steady state at about the same levels as in the studies of Jung et al (Jung et al. 1988) and Willis et al (Willis et al. 1979), respectively.

9.5 Adverse events

9.5.1 Regional analgesia (study III)

A noteworthy observation in study III was that altogether 14 patients experienced moderate to severe respiratory depression. These complications could be explained by the relatively high doses of opioids in these patients. Indeed, it was noted that nine of the 14 patients with respiratory depression symptoms had taken 1.5 – 2 times the mean average opioid consumption observed in the study. According to previous research findings possible predisposing factors for respiratory depression include obesity and hypertension (Chung and Crago 1982). Respiratory acidosis and hypoxia may be detrimental for patients who have cardiac problems due to an increase in hypoxic pulmonary vasoconstriction that may lead to cardiac failure (Lindgren et al. 1991). Further, acidosis may also potentiate the cardiotoxicity of bupivacaine (Covino 1998). The incidence of complications after the epidural catheteri-sation was low and only two patients had to be removed from the study group because of unsuccessful catheterisation. This conforms with the findings of the study by Giebler and colleagues in which the overall incidence of complications after thoracic epidural catheterisation was 3.1% (Giebler et al. 1997).

9.5.2 Intrathecal morphine (study V)

In study V, sporadic episodes of respiratory depression, ranging from moderate to severe, were observed more frequently in the i.t. Mo group. Interestingly, Gray and co-workers reported good postoperative analgesia after thoracotomy with the same i.t. Mo dose (10 µg/kg) as used in study V. Gray and co-workers administered the i.t. Mo dose postoperatively and only one case of respiratory depression was observed among their group of 50 patients (Gray et al. 1986). Neustein and Cohen also noted only one

case of respiratory depression among their 16 patients who were given i.t. Mo (12 µg/kg) at induction of anaesthesia for postthoracotomy pain (Neustein and Cohen 1993). Unfortunately, in these two studies, unlike in study V, no PCA was used and the evaluation of pain was observer-rated.

There appear to be only three reports dealing with post-sternotomy pain in MG patients in the literature (Ferretti et al. 1987, Jahr and Bjerke 1991, Kirsch et al. 1991), even though the epidural technique has been recommended as the method of choice for pain relief after transsternal thymectomy in MG patients (Drachman 1994). Of these three previous reports only the study by Kirsch et al is a controlled study (Kirsch et al. 1991). The findings demonstrated improved postoperative ventilatory function due to use of preoperative lumbar epidural morphine in MG patients undergoing transsternal thymectomy. Two out of 9 patients in the epidural group and 3 out of 10 in the placebo group needed mechanical ventilation for up to 3 days after surgery. Four out of 9 patients in the epidural group and 6 out of 10 in the placebo group could not be extubated immediately (Kirsch et al. 1991). Taking into account the earlier reports and the high frequency of postdural puncture headache found in study V, epidural morphine analgesia might be a better choice for poststernotomy pain in MG patients, assuming that ventilatory function can be restored to the same degree as with i.t. Mo.

In study V, the incidence of postdural puncture headache, the intensity of which exceeded that of poststernotomy pain, was unusually high (4/10) when compared with previous reports (Gray et al. 1986, Neustein and Cohen 1993, Horlocker 2000). After the second patient had complained of significant headache the size of the needle used was reduced to 27G in order to prevent postpuncture headache. Despite this adjustment headaches were still observed. Based on findings in previous studies young age (mean age: 35 ± 3.4 year), female gender and the needle configuration used may have been possible predisposing factors for postpuncture headache in study V (Gielen 1989, Lynch et al. 1992, Horlocker 2000).

9.6 Chronic pain after thoracic surgery (studies I and VI)

The incidence of chronic pain after thoracic surgery has been analysed in a few studies. The reported incidence of persistent postthoracotomy pain syndrome (PTPS) is in the range of 22 – 67% (Kanner et al. 1982, Matsunaga et al. 1990, Dajczman et al. 1991, Landreneau et al. 1994, Bertrand et al. 1996, Katz et al. 1996, Obata et al. 1999) whereas in recent studies the incidence of chronic post-sternotomy pain after cardiac surgery and transsternal thymectomy has been reported to be about 30% (Kalso et al. 2001, Meyerson et al. 2001).

The incidence of PTPS is reported to be 30 – 65% after posterolateral thoracotomy (Landreneau et al. 1994, Obata et al. 1999) and 20 – 60% after VATS (Landreneau et al. 1994, Bertrand et al. 1996). This concurs well with our results after anterolateral thoracotomy with a PTPS incidence of 44% in study I and 61% in study VI.

It can be speculated that more tissue injury causes more pain after surgery (Kavanagh et al. 1994a). Patients undergoing posterolateral thoracotomy have been found to have a higher degree of intercostal nerve impairment compared with patients undergoing muscle-sparing thoracotomy (Benedetti et al. 1998), which indicates that one of the most important differences between the two operative procedures lies in the neuropathic component of postoperative pain. The patients undergoing non-serratus-sparing antero-axillary thoracotomy had better pulmonary function during the first week after surgery and significantly reduced chest pain up to six months after surgery than patients undergoing posterolateral thoracotomy (Nomori et al. 1997). The patients undergoing VATS

for pulmonary resection had less pain and subjective shoulder dysfunction compared with patients having thoracotomy when assessed less than one year after surgery (Landreneau et al. 1994). In both groups the pain medication requirements were similar. Intercostal nerve damage after thoracotomy is most likely a major factor in the development of PTPS, although the exact mechanism is not known (Rogers and Duffy 2000). Interestingly, in a recent study conducted in thymectomy and coronary artery bypass grafting (CABG) patients the localisation of chronic pain after sternotomy was dependent on the type of operation (Kalso et al. 2001). After thymectomies chronic pain was located mainly around the sternotomy scar whereas after CABG pain was also located in the arm, shoulder and/or leg. Various hypotheses have been postulated to explain the chronic pain after sternotomy, i.e. intercostal neuralgia or neuroma caused by the inserted sternal wires for example (Meyerson et al. 2001) but the mechanism of the pain is not yet fully understood.

Higher consumption of analgesics after surgery could be an indication of more severe pain rather than of inadequacy of postoperative pain management (Tammisto 1978). In this respect PCA would be a more reliable method than the more conventional treatment that was used in studies I and VI. However, high consumption of analgesics or more acute pain could also signal a lower pain threshold, which could also be reflected in the reports of chronic pain. This differentiation was examined in the study by Katz and co-workers (Katz et al. 1996) and Kavanagh and co-workers (Kavanagh et al. 1994b) but due to the small number of patients no conclusions could be drawn from these studies.

It has been suggested that peri- or postoperative use of NSAIDs can decrease the incidence of chronic postthoracotomy pain (Sabanathan 1995). However, in study VI the patients who had persistent postoperative pain 6 months after thoracotomy had consumed more NSAIDs during the immediate postoperative period than the patients without persistent pain. Again, the higher consumption of NSAIDs may indicate more pain experienced by the patients. The role of NSAIDs or any analgesic intervention should be studied in a different set-up with standardised comparison of the treatments.

In studies I and VI parenteral opioids, intraoperative intercostal blocks and NSAIDs were used mainly for treatment of pain during the immediate postoperative phases. Thoracic epidural analgesia for treatment of postthoracotomy pain combined with adequate oral pain medication during the first postoperative week and with effective pain management at home resulted in a lower frequency of PTPS than in studies I and VI (Tiippana et al. 2003). Presumably the best method to avoid PTPS is multimodal analgesia during the first postoperative days and regular follow-up of the patients after discharge from the hospital combined with the possibility of contacting the hospital in case of problems in pain management.

Chronic postthoracotomy pain is a combination of many components (Ashburn and Staats 1999). Probably the most severe form of pain is caused by intercostal neuralgia, the incidence of which is reported to be between 1 and 3% (Conacher et al. 1986). Severe pain was reported by 4 – 5% of the patients in study VI and this incidence remained for 12 months. This may represent the severe treatment resistant pain that is seen by pain specialists. Chronic long-term pain may also be a sign of recurrence of malignancy (Kanner et al. 1982). In fact, one of the problems when analysing the patient data in study VI was the high proportion of 25% of patients who were lost to follow-up because of premature death before the end of the study. Excessive spreading of the ribs using thoracic retractor can result in posterior rib fractures at the costovertebral junction and in painful costochondral separations anteriorly (Hazelrigg et al. 1991, Landreneau et al. 1994). VATS approaches can also be associated with significant local trauma to the chest wall structures that can

result in chronic pain (Landreneau et al. 1994).

Throughout the present studies, the patients themselves expressed how important they consider postoperative pain treatment following thoracic surgery. In fact, this is clearly demonstrated by the high response rate of 82 – 89% in both studies I and VI. There was a high incidence of persistent pain which was reported by 45 – 60% of the respondents in these two survey studies, and one can speculate that patients may have been prompted to respond in the expectation that they might receive some further treatment for their pain. Indeed, some patients expressed a wish to be further examined and treated for the pain.

9.7 Future

An integral part of the design of any analgesic regimen after thoracic surgery should be to allow the patient to take deep expansive breaths, cough effectively enough to clear airways and shift accumulating secretions, and to cooperate with physiotherapy in so called "stir up" regimens.

Probably the most noteworthy developments in the treatment of postthoracotomy pain will occur in the field of surgery with the increasing use of less traumatic operative methods, i.e. thoracoscopy. Nevertheless, special attention should also be given to adequate postoperative pain treatment after thoracic operations. At the present time and in the near future the method of choice will probably be multimodal analgesia, i.e. combination of various analgesic techniques such as regional analgesia, systemic use of opioids, and other drugs such as NSAIDs, α_2-adrenergic agonists and NMDA-antagonists (Chia et al. 1998, Tschernko et al. 1998, Tan et al. 1999). A well-tailored postoperative pain control regimen requires careful consideration of the possible risks and benefits to the patient. If effective but invasive methods such as epidural or i.t. opioids and local anaesthetics are not feasible, continuous infusion of an NSAID, e.g. diclofenac or ketorolac, during two postoperative days following thoracic surgery appears to be a valuable alternative as it significantly reduces morphine consumption and improves analgesia. The role of COX-2 in central sensitisation and the effectiveness and safety of selective COX-2 inhibitors will most likely be intensively studied in the future (Katz 2002).

Chronic pain is equally common following surgery for benign and malignant disease. It can be anticipated that more effective methods of acute pain management, e.g. pre-emptive analgesia, epidural infusions of analgesic drug combinations, will reduce the incidence of chronic postthoracotomy pain (Møiniche et al. 2002). As postoperative pain after thoracic operations may last up to six months and may even become chronic (Kalso et al. 2001), patients should be advised to contact their doctor if the pain does not decrease or if it gets worse after primary healing of the wound. It is important that postoperative follow-ups are continued after the patients have been discharged from hospital.

10 CONCLUSIONS

1. Acute postthoracotomy pain is usually severe, may require high doses of opioids and can last several days. Postthoracotomy pain is especially severe when the patient moves or coughs.

2. I.v. diclofenac and ketorolac improved analgesia and significantly reduced morphine consumption after thoracotomy. They were safe with regard to both haemostasis and renal function. However, NSAIDs should be used cautiously in patients who are at high risk of developing renal problems during surgery. Special attention should be paid to fluid balance and urine output. None of the three local anaesthetic techniques, i.e. intercostal, epidural or paravertebral, provided good pain relief after thoracotomy. The required PCA-doses of morphine were high and respiratory depression occurred in one-third of the patients.

3. In MG patients i.t. morphine provided effective poststernotomy pain relief and significantly improved ventilatory function when compared with PCA morphine during the first 24 hours. The high frequency of postpuncture headache was a serious disadvantage. Careful postoperative monitoring is needed during the first 24 postoperative hours because of the compromised muscle strength in MG patients and the possibility of respiratory depression due to pain therapy.

4. Chronic postthoracotomy pain is a major problem. With an incidence of 50% it is equally common following surgery for benign and malignant diseases. Chronic pain after thoracotomy is associated with higher consumption of NSAIDs during the first five postoperative days, i.e. patients, who experience more pain during the first week after surgery are at higher risk of developing a postthoracotomy pain syndrome than other patients. More studies are needed on the epidemiology and treatment of chronic postthoracotomy pain.

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