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Local Anesthesia for Pain Relief after Surgery

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ABSTRACT

Postoperative pain is a common problem in spite of increased awareness among patients and healthcare professionals. The prevailing practice is still to administer opiates, which have a good painrelieving potential but opiates also have a number of negative sideffects. In this Thesis I have analysed the use of local anesthetics in various forms as an alternate means of painrelief after surgery.

Paper I: Twentyone patients operated with an open cholecystectomy received an intrapleural catheter for administration of bupivacaine-adrenaline in various dose regimens. Pain relief and ventilatory parameters were recorded before and after administration. Plasma concentration of bupivacaine was assessed. A double-blind comparison was made in six of the patients. Five patients received an injection of local anesthesia with contrast to determine the distribution of the fluid within the pleura.The intrapleural treatment resulted in an effective pain relieving effect with an improved pulmonary function. The local anesthetic was distributed dorsally in the pleura from the base to the apex. No patient in the placebo group experienced pain relief or improved lungfunction, while the patients in the treatmentgroup were improved. **Paper II:** Twenty patients operated with open cholecystectomy received an intrapleural catheter for postoperative painrelief. The studied parameters were: analgesic effect (n=20), temperature and pain sense (n=20), cutaneous bloodflow (n=9) and phrenic nerve stimulation (n=4). All patients reported reduced pain scores after treatment with 20 ml 0.25% bupivacaine, eleven patients had a loss of their temperature sense on the right side and of these ten also lost their pain sense after treatment, but all had reduced VAS scores. A sligh t increase in blood flow was recorded without difference between the sides, the phrenic nerve was not affected by the local anesthetic. **Paper III:** Twenty males undergoing inguinal hernia repair were subjected to treatment with infiltration of ropivacaine postoperatively. Ten patients received 300 mg and ten 375 mg in a double blind design. VAS scores and consumption of additional anlgesics were followed. Plasma concentrations were determined as well as blood samples and a close monitoring of adverse events was instituted. Both groups reported similar reduction of VAS scores and both groups required the same amount of additional analgesics. Plasma concentrations of ropivacaine were well below the estimated toxic levels and no patient reported any advrse events attributable to the local anesthetic. **Paper IV:** In a multicenter trial the efficacy of 300 mg ropivacaine was compared to 100 mg bupivacaine given as infiltration anesthesia after inguinal hernia surgery. The study comprised 144 patients operated in four hospitals. VAS scores and request for additional anlgesics were recorded, and ability to perform activities of daily life were followed as well as safety parameters. Both drugs proved to be effective in reducing postoperative pain without any difference between the two tested drugs. No adverse events causally related to the local anesthetics were found. **Paper V:** Ninety patients operated with breast conservative surgery and axillary clearance, for malign breast tumors were allocated to three groups. One received infiltration with 20 ml bupivacaine 0.5%, one topical application of 10 grams of Emla cream, and one group served as control. All patients received a PCA device for self administration of morphine in a pre programmed mode. Very little difference was found between the groups, only when analyzing the patients with highest pain scores could a beneficial effect be seen with the local anesthetic treatment. The clinical relevance of this finding is limited.

Papers included in the Thesis

The papers are referred to by their roman numerals in the Thesis as indicated below:

I. Brismar B, Pettersson N, L. Tokics L,. Strandberg Å, Hedenstierna G. ***Postoperative analgesia with intrapleural administration of bupivacaine-adrenaline***. Acta Anaestesiol Scand 1987: 31: 515-520.

II. Pettersson N, Perbeck L, Brismar B, Hahn, RG. ***Sensory and Sympathetic Block During Interpleural Analgesia.*** Regional Anesthesia 1997: 22: 313-317.

III. Pettersson N, Emanuelsson B-M, Reventlid H, Hahn RG. ***High-Dose Ropivacaine Wound Infiltration for Pain Relief After Inguinal Hernia Repair.*** Regional Anesthesia and Pain Medicine 1998: 23: 189-192.

IV. Pettersson N, Berggren P, Larsson M, Westman B, Hahn RG. ***Pain Relief by Wound Infiltration With Bupivacaine or High-Dose Ropivacaine After Inguinal Hernia Repair.*** Regional Anesthesia and Pain Medicine 1999: 24: 569-575.

V. Pettersson N, Perbeck L, Hahn RG. ***Efficacy of Subcutaneous and Topical Local Anesthesia for Pain Relief after Surgery for Malign Breast Tumors.*** European Journal of Surgery; in press.

CONTENTS

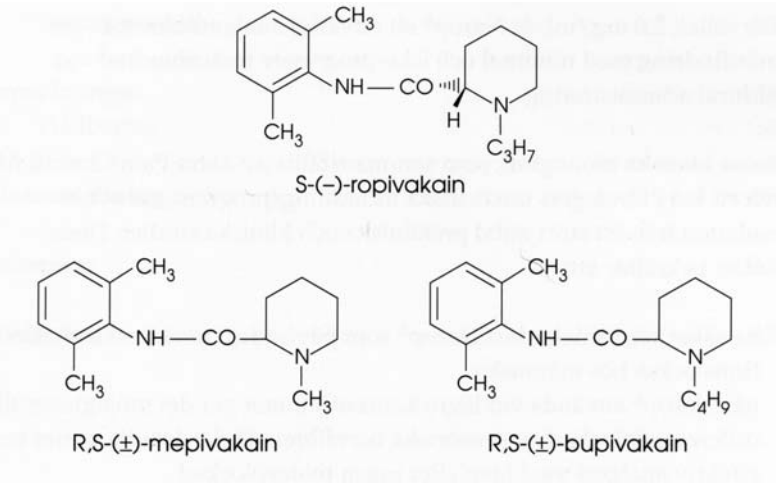
INTRODUCTION

Local anesthesia

Local anesthesia has its origin in South America, where the natives have had knowledge of the properties of the coca leaf for many centuries. The leaves from the Erythroxylon Coca, when chewed, have a pain reducing effect as well as a centrally stimulating effect. Chewing the leaves during long walks in the mountains produced not only increased stamina and less need for food but also pronounced circumoral numbness. The documented history of local anesthesia starts in 1860 when Niemann isolated and described the effect of the alkaloid cocaine, a benzoic acid ester. Carl Koller described the first clinical application in 1884 (Koller 1884), when cocaine was used as a topical local anesthetic of the eye, and thus started the modern history of local anesthesia in clinical practice. Koller was active in Vienna at the same time as Sigmund Freud, and Freud apparently also took part in the related research of cocaine (Honegger 1970). In 1905 Einhorn reported the synthesis of procaine and in 1930 tetracaine appeared as the most potent ester of the benzoic acid. The breakthrough came when Löfgren in 1943 synthesized lidocaine, which is not an ester but an amide derivative (de Jong 1994). Subsequent changes in the structure of the local anesthetic has led to changes in the properties of the agent, aiming at less toxicity and in some agents longer duration of action (Biscoping 2000).

Since the 1960s bupivacaine has dominated in applications where long duration and high doses are necessary, as is the case in obstetric practice and for surgical procedures. This is due to the relatively low cumulative toxicity of bupivacaine, however if accidentally given intravenously there is still a risk of CNS and cardiac side-effects. Bupivacaine is derived from pipecholyl xylidine and was first synthesized by af Ekenstam (Ekenstam 1957), and like most other modern local anesthetics bupivacaine is a chiral drug, possessing a single asymmetric carbon atom. These drugs exist as two enantiomers or stereoisomers, meaning they are mirror images of each other, and when produced come in a 50-50 mixture of the two forms. The two different forms are termed L- or D-, as in laevo and dextro, or in recent terminology, S- and R- meaning sinister and rectus. In 1972 Åberg demonstrated that L-bupivacaine is less toxic than the R-form and since then there have

been many studies showing a similar tendency; that of the two possible stereo isomers R- and S-, it seems that the S-enantiomers are longer acting and less toxic than the R-enantiomer (Åberg 1972, Aps 1978,Fairley 1981, Reynolds 1997). This have led to the development of the amide type S-enantiomer ropivacaine, a homologue of bupivacaine, and lately also the S-enantiomer of bupivacaine.



The range of surgical procedures that can be performed under local anesthesia alone has increased over the years. The inherent advantages are the decrease of patient stress response, thereby minimizing negative changes in fluid and electrolyte balance and inflammatory response, and also eliminating the need for mechanical ventilation. Thereby the patient is exposed to a lesser risk and less inconvenience.

Pain

The International Association for the Study of Pain has defined pain in the following way: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Merskey 1979). From this definition it is clear that pain is a multi-modal entity, an end result of diverse input conditioned by the individuals constitution and prior experience (Taenzer 1986, Morley 1993). In our clinical setting the origin of the pain is quite clear: the surgical trauma. Historically pain was the major obstacle in performing successful surgery, limiting procedures in time. The most important quality of a surgeon was how fast he could perform the operation. It was only with the advent of ether

anesthesia that surgery could start to develop. However, the resulting postoperative pain has historically been regarded as inevitable and something that the patient will have to accept as an effect rather than a side effect. The awareness among physicians of pain as a potentially avoidable symptom has increased over the last decades, and today our approach is much more active. There is also a corresponding increased demand among patients to receive appropriate, available pain-relieving treatment. Pain is to a much lesser degree tolerated by patients and health-care professionals. New methods have been developed and also implemented, new drugs have been introduced, and even a new subspeciality has evolved in anesthesiology with the introduction of specialized pain-teams or "acute pain service". Pain-teams deal not only with postop or post trauma pain but also with chronic conditions and the team consists of persons who are experts on many diverse methods with the common denominator being the aim of reducing pain.

The practicing surgeon performing ambulatory day-surgery, who is just as devoted as the pain-team to free his patients from suffering, has to deal with postoperative pain without the aid of a specialized service. He is faced with the task of sending a newly operated patient home with at least a tolerable pain but preferably pain-free. The day-surgery cases have increased both in numbers and magnitude, in response to the economic realities and the demand from patients who do not wish to spend time in a hospital bed if this is not necessary. The armaments at hand for the surgeon is not as extensive as that of the anesthesiologist in the postoperative ward, as he has to take into consideration that the patient will be without professional monitoring once he leaves the unit and goes home. The methods employed will have to be safe, easy to apply and essentially without side effects, apart from being effective and of long duration at reducing or eliminating pain. Local anesthesia is a mainstay in this effort.

Pain reception

Pain originating from a surgical trauma, postoperative pain, where tissue have been damaged, is termed nociceptive pain as opposed to neurogenic pain where neurotissue has been damaged (Ness 1990). Nociceptive pain is mediated by a group of receptors reacting to harmful or potentially damaging action. These receptors have a higher threshold than sensory receptors and are appropriately called nociceptors and when they are activated we

experience pain (Burgess 1973, Raja 1988, Campbell 1989). Nociceptors are found in the skin, in muscles, ligaments, joints, organ capsules and vessel walls (Raja 1988), and consist of Aò- and C-fibers. Aò-fibers are thin myelinated fibers and have a high conduction velocity while C-fibers are unmyelinated with a lower conduction velocity (Yaksh 1982). Stimulation of Aò-fibers result in a localized precise pain, while stimulation of C-fibers result in a more dull, burning pain (Collins 1960). The afferent neurons from the periphery have their cell nuclei in the dorsal root ganglia in the spinal cord through which they reach the CNS (Yaksh 1982), but also monosynapse reflexes are elicited.

Visceral organs have mechanical type receptors that react to isometric contractions and chemoreceptors that respond to exposure to harmful chemicals (Ness 1990). Pain originating from viscera is of a diffuse and dull character in part due to the rather low density of receptors. The afferent signals from visceral pain receptors run to the CNS mainly by vagal, splanchnic and pelvic nerves but also through segmental nerves.

Postoperative pain is due to both activation of nociceptors in the skin (Raja 1988) and activation of receptors in the damaged visceral structures (McMahon 1995). Experimental data indicate that the visceral component is of a lower dignity and that the major part of the pain originates from the nociceptors in the cutis and subcutis (Scott 1988, Wallin 1988). Local anesthesia applied as infiltration at the site of surgery, inhibits the propagation of the nerve impulse by blocking the sodium channels of the nerve fiber prohibiting the generation of action potentials (de Jong 1994).

Postoperative pain relief

In clinical practice postoperative pain relief is achieved mainly through intra-muscular administration of morphine, and sometimes by infiltration of local anesthesia, either given directly to the operative site or as a regional modality with an indwelling catheter as epidural analgesia with a top-up possibility, supplemented bt oral NSAID. The main criteria for these different agents or methods are collected in table 1.

Postoperative pain appears as a result of the surgical trauma and remains a major unresolved problem for too many patients. In this study pain after open

cholecystectomy (**papers I and II**), after inguinal hernia repair (**papers III and IV**) and after breast-surgery with axillary clearance (**paper V**) has been investigated.

Table 1.

	Advantages	*Drawbacks*	*Cost*
Morphine	Effective pain relief	Sedation. Respiratory depressant. Nausea common. Needs surveillance. Addiction. GI and urinary ret.	Low
NSAID	Can be administered orally. No surveillance needed, can be used for out-patients.	Pain relief sometimes incomplete. Increased risk for GI bleeding complications.	Medium
LA infiltration	Effective pain relief. Few side effects. Target treatment. No central effect. Antimicrobial.	Experience needed for optimal effect.	Medium
LA epidural	Effective pain relief. Top up possibility.	Requires anesthesiologist. Micturition problems. Hypotension.	High

AIMS OF THE PRESENT STUDIES

The overlying aim of the present thesis is to investigate, in various forms, the potential of local anesthetics control postoperative pain and to some degree investigate effects, routes of action, and also the potential, of newly developed forms of local anesthetics. Furthermore emphasis has been put on methods that can be employed by the operating surgeon without the mandatory aid of an anesthesiologist. More specifically the addressed issues in the different studies are listed below.

I. To evaluate the efficacy of intrapleural local anesthesia after high abdominal surgery, especially open cholecystectomy.

II. To study the routes of action responsible for the pain relieving effect of intrapleural anesthesia.

III. To investigate whether the alleged lower toxicity of ropivacaine will allow the utilization of higher doses for pain relief after hernia surgery.

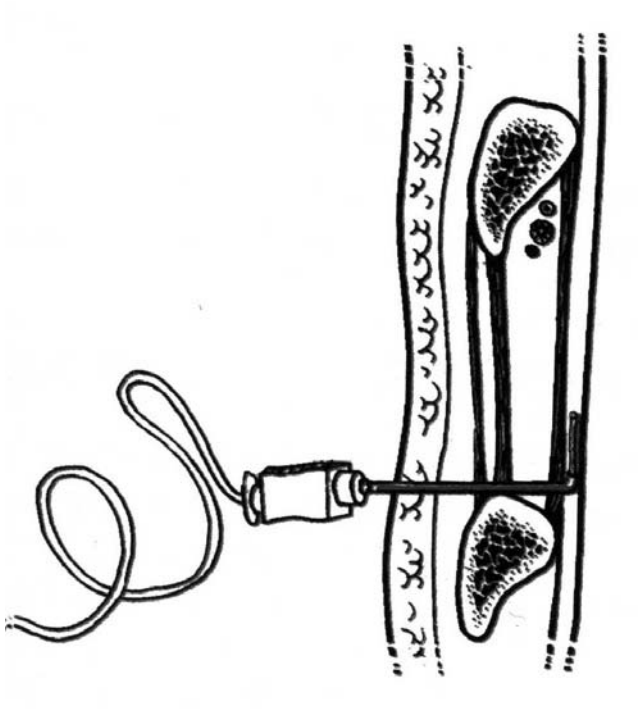
IV. To compare the efficacy of ropivacaine with the presently most widely used long-acting local anesthetic bupivacaine, for pain relief after hernia surgery.

V. To compare the analgesic effect, after surgery of the breast and axilla, of two different modes of application of the local anesthetic; topical or by infiltration.

METHODS

Interpleural (or Intrapleural) catheterization and subsequent instillation of local anesthetics, for the management of postoperative pain was first introduced by Kvalheim and Reiestad in 1984 (Kvalheim1984). The authors noted that some inter-costal blocks, performed to lessen pain after thoracic trauma, were remarkably more effective than others, and they eventually concluded that this was due to accidental deposition of the analgesic compound into the interpleural space. The technique has later been developed to include the placement of an indwelling catheter inside the pleural space, allowing repeated administration.(**Papers I and II**)

With the patient in a lateral position, with the side to be treated up, the seventh inter-costal space is identified. The area is infiltrated with local anesthetic, a 16 gauge Touhy needle is then advanced to a position just superficial to the ribs, the mandrin is withdrawn and a wetted glass syringe is attached. The needle is advanced until the plunger is drawn in by the negative pressure in the pleural space, now the syringe is removed and an epidural catheter, outer diameter 1.1 mm, is introduced through the needle and directed dorsally. The needle is removed and the catheter is connected to an antibacterial filter and to a stop-cock. Alternative methods of introduction into the pleural space have been suggested e.g. the hanging drop method. When the catheterization is performed on awake patients, the patients were instructed to hold their breath with an open airway after a submaximal inspiration. If the catheter is introduced while the patient is under general anesthesia, the procedure is performed during prolonged expiratory apnea. A routine chest radiogram is performed to check for pneumo-thorax.



Placement of an intrapleural catheter

Spirometry was performed to determine the effect of the analgesia on forced expiratory vital capacity, FVC, and forced expiratory volume in one second, FEV 1.0. (**Papers I and II**). The measurements were carried out using a portable unit, Vitalograf, equipped with a paper recording unit. All measurements were made with the patients in a standardized semi-recumbent position. Baseline measurements were carried out pre-operatively, and after surgery measurements were performed before and 15 minutes after administration of analgesia. Recorded values were calculated as the mean of three consecutive measurements.

In order to evaluate the efficiency of a postoperative pain relief regimen it is necessary to obtain a measure of pain intensity and of pain relief. Pain is difficult to measure since there is a marked inter- and intraindividual variation.

Pain assessment with the Visual Analogue Scale (VAS) (Keele 1948, Revill 1976, Scott 1976, Ohnaus 1975) has been used extensively throughout this Thesis (**papers I through V**). This graphic method of rating has its origin in the field of psychology where it has been applied since the early 20th century (Freyd MJ 1923, Aitken 1969), to measure unmeasurables like personality, depression and sleep. Other methods of measuring e.g.

visible manifestations as interpreted by the staff have been shown unreliable (Lim 1968), likewise verbal rating in steps like "mild, moderate, severe and agonizing" has the advantage of simplicity but lacks sensitivity (Huskisson 1970). The VAS scale as it is used today consists of a ruler with a sliding marker on. One side is marked over 10 cm with zero being denoted as "no pain" and 10 denoted as "worst imaginable pain". The patient is instructed to evaluate their present pain as lying somewhere along this line. Compared to other means of evaluating pain the VAS scale has shown good correlation to the level of pain. (Huskisson 1983, Price 1994). In **papers I and II** VAS was tested before and 20 min after administration of intrapleural local anesthetic, in **paper III** VAS was evaluated at both rest and on mobilization at fixed intervals during the examination period, and in **paper IV** VAS was evaluated in three different modes; rest, mobilization and coughing. In **paper V** VAS was only registered at rest and then at fixed time intervals.

In **paper I,** ***Plasma concentrations*** of bupivacaine were assessed using a standard gas chromatography technique (Mather 1974), in **paper III** bupivacaine and ropivacaine were measured by gas chromatography with a nitrogen-sensitive detector (Björk 1990). Plasma concentration of acid alpha-1-glycoprotein (AAG), the protein that bind to local anesthetics, was determined by a radial immunodiffusion technique (Mancini 1965). Since the systemic toxicity of local anesthetics is known to be related to the free drug plasma concentration, the AAG values served as a relative indicator of potential systemic toxicity of ropivacaine (Tucker 1988).

Computerized tomography (CT) was performed on five patients in **paper I**, with injection of a contrast-medium in the intrapleural space (Omnipaque 180) , to visualize the distribution of the local anesthetic agent. In **paper II** CT was performed in four patients to determine the effect of intrapleural local anesthetic on the phrenic nerve, and hence the position of the diaphragm.

Thermal thresholds in the skin were measured to indicate the effect of intrapleural local anesthesia on pain and temperature sense in **paper II**. After a wash-out period of eight hours without injection in the intrapleural catheter the patients normal pain and temperature sense was established with a thermotest-device (Thermotest, Somedic Production AB, Stockholm) with an examining probe with an area of 25 x 50 mm. The

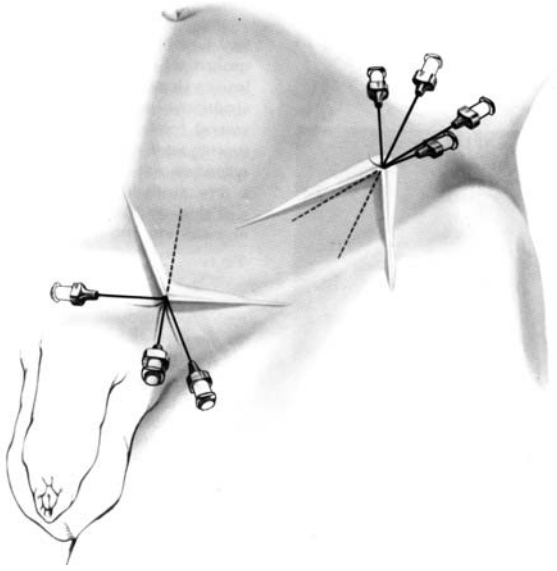
probe produces increasing cold or heat rapidly from a baseline of 30 deg C. (Fruhstorfer 1976). The measurements were repeated after injection of 20 ml of 0.25% bupivacaine into the intrapleural catheter. The probe is placed on the area to be tested, and as soon as the patient experiences a change in temperature he/she presses a switch and the change is reversed. To test the pain-sense the cold, or heat, is increased and the patient is instructed to press the switch when a sensation of pain is felt, and the reached values are recorded. If the patient fails to indicate hot or cold in spite of a change of five degrees C at repeated measures, the result was considered to represent abnormal temperature-sensitivity. Likewise, if the patient did not indicate hot or cold pain at 50 and 10 degrees C respectively, this was considered indicative of abnormal pain-sensitivity.

Cutaneous blood flow changes, as an expression of sympathetic block, was investigated with three different methods in **paper II**. These methods were cutaneous temperature measurements, Laser Doppler flowmetry, and fluorescein flowmetry. In all three methods the abdomen was divided into four sections on each side of the midline. The sections were of equal length from the clavicle to the inguinal ligament.

Cutaneous temperature was determined using an electronic thermometer. (Universal TE 3, Ellab Instruments A/B, Copenhagen, Denmark). Laser Doppler flowmetry measures the skin blood flow as the frequency shift that is caused by the number and velocity of moving red blood cells (Holloway 1977, Nilsson 1980, Bengtsson 1983). We employed a Periflux PF 1c (Perimed AB, Järfälla, Sweden). The third method used was Fluorescein flowmetry (Perbeck 1985). Sodium fluorescein was given as an intravenous bolus injection and the time required for the fluorescense to increase from 10% to 90% of the maximum intensity was used as an index of the blood flow. The fluorescense is detected by repeated photographs of the area to be examined and then by determining the density of the negative exposed film, hence increased density correlates to increased fluorescense. The first three patients received fluorescein before and after administration of la. Due to problems in evaluating the fluoresence at the second injection, with a lingering background fluorescence still detectable from the first injection, instead the difference in blood flow was estimated from the difference between the treated and the non treated side, thereby also eliminating the interindividual biological variation.

Phrenic nerve stimulation. The phrenic nerve runs along the lateral aspect of the vertebral column just beneath the pleural sac. To establish whether intrapleural local anesthesia affects this nerve, we carried out a functional test in four patients in **paper II**. With the aid of a nerve stimulator (Medelec MS91, Medelec, Surrey, England) connected to a bipolar electrode, the phrenic nerve was stimulated between the two heads of the sterno-cleido mastoid muscle on the right side. Stimulation was applied at 100-200 V as squarewave pulses of 200 microseconds duration with a rate of 10 Hz. The response in the diaphragm could be observed as a change in the configuration of the epigastric area and also be recorded on the Medelec equipment by placing one electrode over the xiphoid process and the other over the eighth rib (Hedenstierna 1994).

Tissue infiltration. Local anesthestic was injected (papers **III, IV, V**) into the cutis and subcutis utilizing a 20 ml syringe with an intramusclar needle. The local anesthetic agent was evenly distributed along the edges of the incision and in the adjacent subcutis and spread in a sun-fan like fashion. In paper **III** and **IV** half the volume was injected as above and the other half was distributed around the ilioinguinal nerve, the neck of the hernial sack and in the surrounding muscles, whereas in **paper V** the whole amount was injected around the incisions in the subcutis.



Infiltration for hernia repair

Patient Controlled Analgesia (PCA) is a relatively new technique for postoperative pain management. It was used in **paper V** of this Thesis to determine if locally applied anesthetics has a potential to decrease the consumption of morphine. PCA was developed in response to a growing awareness of the large numbers of patients not receiving adequate pain relief in spite of treatment with potent drugs, mainly opioids. The basic idea of the PCA method is that the patient can administer a predetermined dose of the prescribed agent, without the delay otherwise implied by demanding an injection from the attending nurse. The PCA unit consists of a computerized pump with a built in, rechargeable battery. To this pump a container of a prescribed drug is attached and a line is connected to the patient, usually by a routine indwelling intravenous catheter. The pump computer offers several options and modes of administration. For the standard postoperative patient, a bolus dose is given when the pump is activated, followed by either a background infusion with an option for the patient to administer complementary doses on demand by pressing a handheld button, or without continuos infusion and only "on demand" administration by the patients "button" request. The size of the bolus dose, infusion rate, size of dose per request, lock-out time between doses and maximum delivery is set by the attending physician and depends on the anticipated need of the patient. The PCA computer records all events for later analysis, allowing adjustment of the settings if deemed necessary.

PATIENTS

This Thesis is based on the results from investigations of a total of 295 patients, 115 women and 180 men.

In **paper I** Twentyone otherwise healthy patients, 16 women and 5 men, mean age 45 years (22-68), operated with open cholecystectomy were studied. Nine patients received 10 or 20 ml 0.5%, six patients received 20 ml 0.25% and six patients received 10 ml 0.25% . Five patients received one injection of local anesthetic with contrast. A comparison between active substance and placebo was performed in six patients. In all patients plasma concentration of bupivacaine was determined.

Paper II comprised 20 patients, mean age 42 years (24-81), operated with open cholecystectomy. There were nine women and eleven men. The following parameters were studied: Analgesic effect (n=20), temperature and pain sense (n=20), cutaneous blood flow (n=9), and phrenic nerve stimulation (n=4).

In **paper III** 20 otherwise healthy men, median age 45 years (19-66), planned for inguinal hernia repair, were investigated. In a double blind design ten patients received 300 mg ropivacaine and ten patients received 375 mg ropivacaine. Plasmaconcentration of ropivacaine, VAS scores and consumption of additional analgesics were followed in all patients.

In **paper IV** a multi-center trial, with four participating hospitals, was performed. A total of 144 otherwise healthy men, median age 50 years (24-69), planned for inguinal hernia repair, were included. Half the patients received treatment with 100 mg bupivacaine infiltration analgesia, and the othjer half received 300 mg ropivacaine. The following parameters were followed in all patients: VAS scores, request for additional analgesics, ability to perform activities of daily life and safety parameters.

In **paper V** ninety women with a diagnosed breast cancer, mean age 56 years (30-83), who were planned for curative surgery, were included. Patients were randomly allocated to

treatment with bupivacaine infiltration (n=29), topical application of lidocaine/prilocaine (n=31), or no treatment. All patients received a PCA pump for intravenous morphine administration on demand. VAS scores and morphine consumption were followed.

RESULTS

Paper I:

Postoperative analgesia with intrapleural administration of bupivacaine-adrenaline

This paper addressed several aspects of a novel route for administration of local anesthesia, as well as a comparson with placebo.

Pain relief. Administration of the 5 mg/ml bupivacaine solution resulted in a low VAS (scale 0-10) score of 0-2 in 94 % of the administrations. There was no statistically significant difference between the 10 and 20 ml doses. With 20 ml of 2.5 mg/ml solution a comparable effect was found, but when 10 ml of 2.5 mg/ml was used inadequate pain relief was found.

The onset of the pain relief was very rapid as most patients experienced the effect after a few minutes with a duration of 2-3 hours. Of the treated patients only one demanded additional analgesia. The treatment with the lowest dose, 10 ml of 2.5 mg/ml bupivacaine, was compared to administration of saline. All patients in the treatment group reported good pain relief compared to none in the placebo group.

Ventilatory capacity. The forced ventilatory capacity (FVC) was reduced post operatively by 55% in the first postoperative day and by 34% the second, compared to pre-operative values, measured before intervention with intrapleural bupivacaine. When the local anesthetic was given the FVC increased by 56% day one and 35% day two. The results were the same with 10 ml or 20 ml of 2.5 mg/ml or 20 ml of 5 mg/ml. The forced expiratory volume in one second (FEV 1.0) was improved in a similar way. When the active treatment was compared to placebo, again the active treatment produced a marked increase in FVC and FEV 1.0, 69% and 62% respectively, compared to 0% and 1% when saline was administered.

Dose requirements. The plasma concentration curves showed a steep rise initially, peaking 20-30 min after administration. The mean peak value for 20 ml of 5 mg/ml was 834 ng/ml while for 20 ml 2.5 mg/ml the peak was 758 ng/ml (non-significant difference). In single patients however the values reached an undesirable high plasma concentration, in one patient more than 1700 ng/ml after the first administration and in two others 1900 and 2400 ng/ml after repeated administration. When the concentration was measured after repeated administrations of the lower dose, 20 ml of 2.5 mg/ml, none of the patients showed a peak concentration over 900 ng/ml. No side effects related to the local anesthetic were recorded, special attention was directed at central nervous symptoms, circumoral numbness or cardiac arrhythmia.

Distribution of intrapleural administration. When the distribution of the local anesthetic was studied in five supine patients, using computerized tomography, it was found to be distributed along the dorsal space in the pleural sac, from the apex to the diaphragm.

Complications and safety aspects. In one patient the catheter tip was accidentally placed outside of the pleural space. Four patients developed pneumothorax detected on chest radiograms. The pneumothorax did not give any subjective symptoms and was easily evacuated through the intrapleural catheter. No infections were detected in conjunction with the pleural space or the catheter tips. Control spirometry was performed in 11 patients one month post operatively and did not show any impairment of the lung function compared to preoperative values.

Paper II:

Sensory and Sympathetic Block During Interpleural Analgesia

An examination of the effects of interpleurally administered local anesthesia on intercostal nerves and the thoracic sympathetic chain.

Pain relief. The intrapleural analgesia induced substantial pain relief expressed as reduction in pain score, median VAS (scale 0-10), before bupivacaine was 6.9 (range 2-10) and after 1.1 (range 0-4; P<.001). No supplementary analgesics were required.

Temperature and Pain sense. Of the 20 examined patients 11 experienced a loss of temperature sense and of these, 10 experienced loss of pain sense on the treated right side. All tested patients had a good painrelieving effect of the treatment, and none had any loss of sensation on the left side.

Cutaneous Blood Flow. The skin temperature increased slightly on both the left and right side when intrapleural anesthesia was induced. When blood flow was measured with Laser-Doppler flowmetry a slight increase, also on both sides, was detected, and measurements with fluoresceinflowmetry also indicated a slight increase in cutaneous blood flow on both sides of the trunk.

Phrenic Nerve Stimulation. Stimulation of the phrenic nerve before and after intrapleural analgesia revealed that the treatment did not affect the function of the diaphragm.

Safety Aspects. No pneumothorax was detected, nor were any other complications referable to the intrapleural catheter observed.

Paper III:

High-Dose Ropivacaine Wound Infiltration for Pain Relief after Inguinal Hernia Repair

A comparison of two doses of ropivacaine, with special emphasis on efficacy and safety.

Pain relief. Postoperative pain at rest, expressed as median VAS score (scale 0-100) over 24 hours, was 4 (range 0-40) in the low-dose group and 8 (range 0-69) in the high-dose group. Corresponding figures for pain during mobilization were 20 (0-65) and 17 (0-69). The highest scores during mobilization were recorded at 12 hours and were 36 (15-50) in the low-dose (LD) group and 28 (5-60) in the high-dose (HD) group. These differences were not statistically significant.

Time to first administration of supplementary analgesics was measured as an indirect expression of the duration of the local anesthesia. In the LD group it was 7.6 (range 5-23) and in the HD group it was 5.6 hours (3-23). The number of acetaminophen-codeine tablets per patient during the first 24 hours postoperatively were 5 (2-8) and 6 (2-8). No patient required ketobemidone.

At four hours all patients in the LD group and all but one in the HD group were able to walk around.

Pharmacokinetics. Maximum concentration (Cmax) of ropivacaine was reached between 45 to 60 min after start of infiltration, with almost no decrease in the plasma level during the first two hours. The values were statistically higher in the high-dose group and the highest individual value was 3.0 mg/L. Mean Cmax was 1.5 mg/L (SD 0.4) and 2.2 (0.7) in the LD and HD groups respectively. The highest free plasma concentrations were determined in the 45-min samples for all but one patient, who had the highest level in the 2-hour sample. The highest individual value was 0.28 mg/L (LD). The mean value for the 45 min free plasma concentration sample was 0.12 (0.07) and 0.15 (0.06) for the LD and HD groups respectively. At 45 min the free fraction was estimated to be about 8 %.

The terminal half-life was calculated to be approximately 11 hours (LD) and 15 hours (HD). Concentration of AAG, the protein that ropivacaine predominantly binds to, increased during the 24 hour sampling period. The median concentration before ropivacaine-infiltration was 15 μg/L (range 11-24) and at 24 hours it was 18 μg/L (12-29).

Safety aspects. Bradycardia (< 50 beats/min) occurred in four patients at eleven recorded episodes. The lowest recorded heart rate was 48 beats/min. Two of these episodes coincided with relatively high plasma drug concentrations, 2.5 and 2.9 mg/L. These patients later had new bradycardia episodes without high plasma concentrations.

Other recorded adverse effects in two patients were nausea, vomiting and dizziness. These events occurred without association to high plasma levels and both patients were in the LD group. Two patients experienced transient loss of sensation in the leg on the operated side. This was believed to be secondary to accidental block of the femoral nerve during the infiltration process.

No abnormal ECG findings were seen and only small changes in hemoglobin and platelet counts occurred. The leukocyte count was increased by 25-100 % during the first 24 hours and was still elevated after 12 days. One patient had a 25 % elevation above normal of the liver enzyme SGPT on day 12. No patient had a wound infection or signs of abnormal healing.

Paper IV:

Pain Relief by Wound Infiltration with Bupivacaine or High-Dose Ropivacaine after Inguinal Hernia Repair

A comparison of the standard long-acting local anesthetic, bupivacine, with pure S-isomer ropivacaine.

Pain relief. Pain at rest, on mobilization and when coughing were recorded as VAS scores (0-100). Median VAS scores at rest were between 5.0 and 12.4 for ropivacaine and 5.0 and 14.5 for bupivacaine during the first 24 hours. Slightly higher pain

scores were obtained on mobilization (range 13.7-24.7 and 17.1-24.1, respectively) and on coughing (15.2-20.4 and 19.4-25.2), these differences were not statistically different.

The AUC for the first 12 hours were the same for ropivacaine and bupivacaine. In the ropivacaine group 49% reported wound pain during the first postoperative night, the corresponding figure for bupivacaine was 39%.

Time to the first administration of additional analgesic was 3.6 and 3.8 hours, the number of acetaminophen-codeine tablets per patient was 5 (range 0-12) in the ropivacaine group and 4 (0-10) in the bupivacaine group (ns). Twelve patients in the ropivacaine group and 13 in the bupivacaine group required morphine, and the highest total individual dose was 20 mg.

Patients´ ability to move around was analyzed. Among those who attempted to walk during the first 4 hours, which was only about one third of the total, those in the ropivacaine group could walk around with minor or no problems earlier than those in the bupivacaine group ($P < 0.03$). From two hours and onwards there was a 5-25% higher proportion of the ropivacaine patients who reported this improvement. After 24 hours 93% of the ropivacaine patients and 86% of the bupivacaine patients had experienced only minor or no problems on mobilization at some point in time.

Safety aspects. Three patients (2%) had a serious complication. One patient in the ropivacaine group was kept in the hospital for an additional day due to wound pain (ropivacaine), one patient was diagnosed with acute cholecystitis (ropivacaine) and one patient had low abdominal pain (bupivacaine). These events were considered not to be causally related to the local anesthetics given.

Paper V:

Efficacy of Subcutaneous and Topical Local Anesthesia for Pain Relief after Surgery for Malign Breast Tumors

A comparison between two ways of administrating local anesthesia, by Emla cream and infiltration with bupivacaine, after surgery for breast cancer.

Pain scores and morphine consumption. The mean VAS scores (scale 0-10) for all patients were 2.7, 2.0 and 2.1 for the control group, infiltration group and topical group respectively. Further analysis showed that local anesthetics reduced the proportion of patients with high VAS scores and morphine consumption during the 20-h follow-up period. The 75^{th} percentile for the sum of all 7 postoperative VAS scores was 18.6, 14.3, and 14.6 (mean score 2.7, 2.0 and 2.1) for the controls, the infiltration and topical anesthesia groups, respectively. The corresponding data for the morphine consumption was 24.5, 18.5, and 16.2 mg.

Plots of the higher percentiles for the VAS score over time showed that the difference in postoperative pain was apparent from 6 hr and onwards. A higher VAS score usually implied a higher morphine consumption.

AUCM . The 50^{th}, 75^{th} and 90^{th} percentiles for the average pain over time (AUCM) also tended to show slightly lower values in patients who received local anesthetics, although the differences between the groups were not statistically significant. Since the pain scores and morphine consumption both express pain, these parameters combined were thought to emphasize possible differences between the groups. Such comparisons, which were based on the AUC for VAS (to make the pain score comparable to the morphine consumption) also indicated that pain tended to be lower from 6 hr and onwards in both two groups receiving local anesthetics as compared to placebo.

Patients in worst pain. Differences between the groups were highlighted by exploratory analyses based on exclusion of the patients who were essentially pain-free (AUCM < 0.5). Administration of infiltration or topical anesthesia then significantly reduced most indices of pain, while data were quite similar for the two forms of local anesthesia.

DISCUSSION

Several authors, and indeed numerous patients, bear evidence to the fact that postoperative pain is still an unresolved problem (Rawal Lt 01, Rawal Lt 00, Dahl 00, Frenette 1999, Filos 1999, Rosenberg 1999). Many patients still suffer unnecessarily from the effects of surgery, or the effects of opioid analgesia, where nausea and inability to resume mobilization dominate. Most authors agree that the most successful treatment to eliminate postoperative pain and discomfort is multimodal: a combination of low impact surgery, "tissue tenderness", oral, non opioid drugs and use of local anesthetics. A good, well planned postoperative analgesic regimen will enable the patient to resume early feeding and aggressive mobilization without pain, drowsiness, nausea or other negative side effects. To implement this regimen we need to involve staff at all levels and we need to increase our awareness. Apart from our apparent duty as doctors to relieve pain in our patients, there is also the potential of an improved overall postoperative result (Rosenberg 1999, Kehlet 1997).

As surgeons we tend to leave the postoperative pain relief issue to anesthesiologists, considering our job to be done when the wound is closed. In this Thesis I have tried to show that the use of local anesthetic agents for pain relief after surgery is still developing, and that much of this developing potential lies in the hands of the surgeon. Used in the described ways local anesthesia is a safe and effective analgesic agent that targets pain at its origin, and in recommended doses is virtually free from side effects.

Intrapleural analgesia has not received a widespread use in clinical practice in Sweden, although it has an almost remarkably positive effect on both pain and lungfunction after upper abdominal surgery. The initial works were presented already 15 years ago (Kvalheim 1984, Reiestad 1986, **paper I** of this Thesis). Since then many authors have confirmed these findings, (Kaukinen 1994, Polomani 1993, Sinatra 1991, Frenette 1991, Rademaker 1991, Bragg 1991, Strömskag 1991) showing the superiority of intrapleural administration of local anesthetics compared to opioids, and also to local anesthetic wound perfusion (Russel 1993, van Raay 1992), both concerning the analgesic effect, ventilatory capacity and patient satisfaction. Indeed there have been a few authors who have not been able to show any benefits regarding lungfunction after treatment with intrapleural local anesthetics (Oxorn 1989). Most failures have been reported after thoracic surgery or

thoracic trauma. In combination with thoracic surgery and trauma however, the patho-physiology in the pleural space is fundamentally altered especially there is a profuse effusion of fluid.

In **paper I** we looked at different doses and concentrations of bupivacaine-adrenaline, trying to find the least amount to yield adequate effect. We found that 10 ml of 0.25% bupivacaine-adrenaline had good pain relieving effect, with 43 of 52 administrations resulting in VAS scores of 2 or less. In increasing doses we saw improved efficiency of the pain relieving effect but when 20 ml 0.5% was administered some patients approached toxic plasma concentration levels after repeated doses. Although no patient presented general symptoms of local anesthesia toxicity, it seems prudent to recommend that initial dosage is kept in the lower range. In a study by Seltzer et al 30 ml of 0.5% bupivacaine-adrenaline was administered and plasma concentrations were followed after single dose injection (Seltzer 1987). The resulting mean maximum concentration, 2.07 μg/ml, stayed below toxic levels, but two patients had high values, one of which had seizures. Jorfeldt et al has determined a bupivacaine concentration of 4 μg/ml as the level above which CNS toxicity may occur (Jorfeldt 1968).

The rapid onset and excellent pain relieving effect of intrapleural local anesthetics was initially conceived as a shortcut to a complete unilateral block of the inter-costal nerves. However, reports of ipsilateral Horner´s syndrome after injection into the intrapleural space with the patient in the head down position (Reiestad 1989, Sihota 1988), naturally led to suspicion of involvement of the thoracic sympathetic chain. In our study (**paper II**) we could not show a clear effect on the sympathetic chain expressed as increased cutaneous blood flow, measured with Laser-Doppler flowmetry or Fluorescein flowmetry, neither could we show a pronounced unilateral effect on skin temperature. In a placebo controlled study by Ramajoli on patients with abdominal pain, cutaneous temperature increased on both sides of the abdomen of those patients who received intrapleural bupivacaine (Ramajoli 1998). The authors postulate that unilateral intrapleural administration of local anesthetics causes a bilateral block of the thoracic sympathetic chain as well as a block of the splanchnic afferent nerves. Many studies have shown a pronounced effect on pancreatic pain (El-Dawlatly 1994, Ahlburg 1990, Durrani 1988), thoracic post herpetic neuralgia (Reiestad 1990, Sihota 1988), pain during percutaneous nephrolithotomy, and other forms of chronic pain. The distribution of the local anesthetic

inside the pleural cavity (McKenzie 1996, Strömskag 1990, **paper I** 1986), is along the dorsal aspect, adjacent to the vertebral column immediately over the sympathetic chain and in the sub-pleural space. This leads us to the conclusion that the effect of intrapleural analgesia not only gives a continuous block of intercostal nerves, but also involves block of abdominal sympathetic ganglia and afferent splanchnic nerves passing along the vertebral column.

Different structural characteristics in the chemical composition of local anesthetics result in different properties of the agent, and this have been used to develop local anesthetic drugs for a different purposes. We thus have the possibility to chose a specific local anesthetic best suited for the procedure at hand. For limited surgical procedures of short duration, such as removal of dermal changes, small lipomas and other forms of minor surgery, where the expected resulting postoperative pain is mild, the surgeon would chose lidocaine, prilocaine or carbocaine. These agents are for clinical purposes similar with a rapid onset and a moderate duration. For a procedure that is expected to take longer or induce prolonged post operative pain bupivacaine has been the agent of choice. Bupivacaine is of the amide type, consists of a mixture of two stereo isomers and has a high degree of protein-binding, around 96% (Covino 1986). A high protein binding rate usually implies a longer duration of action due to a stronger attachment to the nerve membrane proteins. A major shortcoming when treating postoperative pain with local anesthetics is the limited duration of action and interest has been focused on developing drugs with a longer pain relieving effect. This is of course of special importance when conducting day surgery, where the patient is out of reach of a second injection. Ropivacaine is structurally intermediate between mepivacaine and bupivacaine but is produced in the pure S-isomer form, and with a plasma protein binding of 90-95% (Wildsmith 1989). Theoretically the pure S-isomer formulation is the basis for the belief that ropivacaine is less CNS and cardiotoxic than bupivacaine, and thus can be administered in higher doses, while the almost identical protein binding rate should give a similar effect-duration. In subsequent studies on animals (Åkerman 1988, Feldman 1988), it has been shown that ropivacaine gives profound infiltration anesthesia with a dose-related duration of action that in animal studies seemed to exceed the properties of bupivacaine. When ropivacaine was tested on human volunteers the findings from the animal studies were confirmed, namely that ropivacaine could be given in higher doses before signs of

CNS toxicity occurred (Knudsen 1997, Scott 1989). The same relationship seemed to be true for cardiotoxicity indicating that ropivacaine is less arrythmogenic than bupivacaine (Knudsen 1997). When studied in clinical settings infiltration with ropivacaine has been shown to exceed bupivacaine with a longer duration of analgesia after inguinal hernia surgery (Johansson 1997, Mulroy 1994) using doses of up to 200 mg.

In an attempt to determine the safety and efficacy of ropivacaine in higher doses after inguinal hernia surgery we used first 300 mg, and after careful scrutiny of the outcome, especially analyzing adverse events, 375 mg was infiltrated in and around the surgical site at the termination of the operation. We found these doses to be safe, efficient and virtually free from side effects. The pain relieving effect, measured as VAS scores, time to first request for supplementary analgesics and total consumption of additional analgesics were better than in comparable studies, where lower doses of ropivacaine had been used. Pain-scores were low both at rest and during mobilization but there was no detectable difference between the two administered doses of 300 and 375 mg.

The next phase in this quest was to compare 300 mg ropivacaine with 100 mg of bupivacaine. The hypothesis was that a longer duration of action on postoperative analgesia would be achieved with a maintained safety level, when a larger dose of an equipotent local anesthetic was administered. In compliance with ethical considerations the study was designed without a placebo arm. We consider it clearly shown by numerous investigators, as well as in longstanding daily clinical practice, that local anesthetics and especially bupivacaine has a good effect on postoperative pain after inguinal hernia surgery (Mulroy 1994, Dierking 1994, Harrison 1994, Bays 1991, Tverskoy 1990). The method of operating inguinal hernias in bupivacaine anesthesia alone has been in practice in our institution at Huddinge University Hospital for 20 years.

The study (**paper IV**) comprised 144 patients operated for inguinal hernias, with random allocation to postoperative treatment with either ropivacaine or bupivacaine infiltration. In this study we failed to demonstrate any effect on duration in favor of ropivacaine in spite of giving three times the dose of bupivacaine. This was an unexpected but important finding indicating that, given in the described way, local anesthesia of the used type seem to have a therapeutic ceiling when nociceptor blocking is almost total. To achieve longer lasting postoperative analgesia we will have to look for other ways of administration or delivery, or completely new and different drugs.

When infiltrating local anesthetic in a surgical wound we aim at blocking the nociceptor-neurons that signal pain to the CNS. Other authors have carried the application of local anesthesia further in refinement, by simply spraying the local anesthetic as an aerosol into the wound before closure, thereby achieving good pain-relieving effect. After inguinal hernia surgery (Sinclair 1988) 200 mg lidocaine was administered, and after hysterectomy (Sinclair 1996) 500 mg lidocaine was administered 500 mg was used. In these placebo-controlled studies the superior pain relieving effect could be demonstrated up to 24 hours postop. In an other study by Holst 200 mg lidocaine was administered as an aerosol after lower mini laparotomy for sterilization with an unsatisfactory result on postoperative pain (Holst 1992).

Simplicity and ease of application has always appealed to surgeons, thus we hypothesized that by creating a depot of local anesthetic superficial to the surgical wound, we could produce a better and longer-lasting analgesia eliminating needles and syringes. Emla® creme (Astra, Sweden), a mixture of prilocaine and lidocaine, has originally been introduced as an aid to venipuncture and venous cannulation in children and other patients especially susceptible to mild pain. When the cream is applied beneath an occlusive dressing the skin barrier is hydrated and penetrated and the local anesthesia reaches the superficial nerve endings beneath within 60 min. We set out to test this method of topically applied local anesthesia after wound closing comparing it to infiltration in and around the wound before closing, in patients scheduled for breast conservative surgery with axillary clearance for breast cancer. With the exception of one study concerning excision of benign breast lumps (Owen 1985) we have not found any studies evaluating the effect of local anesthesia infiltration peroperatively in this patient category so the two regimens were compared to a group receiving no local treatment. All patients received a PCA pump for self administration of intravenous morphine postoperatively when needed. Somewhat surprisingly we failed to detect any benefit of local anesthesia compared to placebo of either of the two methods of delivery, when judged by VAS scores or consumption of morphine. Only when analyzing the subgroup with the most pain, arguing that those who were virtually painfree had no potential for improvement, we could demonstrate a difference in favor of the local anesthetic treatment. In this subgroup of patients, representing approximately two thirds of the whole, we were able to show a pain relieving effect with our intervention. The use of Emla creme for pain relief after surgery has been

studied by Fassoulaki also after breast surgery for cancer (Fassoulaki 2000). The design of that study was quite different from ours and results are not readily comparable, for example they applied twice the amount of the local anesthetic cream at a distance from the surgical incision and kept on applying Emla cream for four days after surgery. Still no difference was noted between the treatment groups regarding immediate postoperative pain, but there was a difference with regard to chronic pain recorded three months postoperatively. We did not address the problem with chronic pain in our study. In absence of indisputable results we feel that there are indications that topical application of local anesthesia as a cream can equal infiltration in some procedures and that the simplicity of the method warrants further studies.

Many problems concerning postoperative pain relief still remain to be addressed by inclined clinicians, not least surgeons. Trials have been made with indwelling catheters permitting continuos or intermittent perfusion of the surgical site with local anesthetics. Oakley et al showed in a randomized trial, that infusion of local anesthetics via a disposable pump system was superior to placebo after hernia repair up to four days postoperatively (Oakley 1988). When Zieren et al tried repeated bolus injections of bupivacaine via an indwelling catheter at six hour intervals however, they could not show a beneficiary effect compared to oral analgesics after hernia repair. Instead they pointed to an increased cost with the indwelling catheter system of £100! (Zieren 1999). In analogy with patient controlled analgesia (PCA) where the patient can administer an analgesic compound, usually opioid, intravenously, a system for self administration of regional analgesia has been studied, appropriately called ”patient controlled regional analgesia” or PCRA. Initial trials on day surgery patients, equipped with a disposable pump system have shown promising results, especially considering the possibility to prolong the local anesthetic effect on demand, by the patient (Rawal 1998). Further advances in the related device manufacture, allowing more sophisticated use by the patient with retained safety, is ongoing. In the field of pharmacology trials with local anesthetics encapsulated in liposomes, allowing a slow release of the local anesthetic, can mean a pain relieving effect of several days from a single deposition (el-Ridy 1999, Bucalo 1998, Lafont 1996).

Meanwhile, we can come a long way towards our goal of improved pain relief and comfort after surgery, by simply applying and implementing existing knowledge and therapies to each and every one of our patients.

CONCLUSIONS

- Intrapleurally administered local anesthetic gives very good postoperative pain relief and also improves ventilatory function after open cholecystectomy.

- The effective pain relief after intrapleural local anesthesia seem to be due not only to a wide intercostal block but also to a partial block of sympathetic and splanchnic nerves.

- Ropivacaine in doses of 300 and 375 mg may be infiltrated in the cutis and subcutis without unwanted side-effects, but without difference in pain-relieving effect between the two doses.

- No difference in pain relief could be demonstrated between 300 mg ropivacaine to 100 mg bupivacaine when infiltrated in the wound after inguinal hernia surgery.

- Local anesthesia slightly reduces pain scores after surgery for breast cancer, but is of clinical value only for those with the highest pain scores.

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REFERENCES

Ahlburg P, Noreng M, Molgaard J, Egebo K. Treatment of pancreatic pain with interpleural bupivacaine: an open trial. Acta Anaesthesiol Scand 1990; 34(2): 156-157.

Aitken RC. Measurements of feelings using visual anlogue scales. Proc R Soc Med 1969; 62: 989-983.

Allvin R, Rawal N, Saros GB. Postoperativ smärtbehandling. Är det dags att avskaffa intramuskulära injektioner? Läkartidningen 2000; 97(14): 1687-1691.

Aps C, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. Br J Clin Pharmacol 1978; 6(1): 63-68.

Bays RA, Barry L, Vasilenko P.The use of bupivacaine in elective inguinal herniorrhaphy as a fast and safe technique for relief of postoperative pain.
Surg Gynecol Obstet. 1991 Dec;173(6):433-7.

Biscoping J, Bachmann-Mennenga MB. Local anesthetics from ester to isomer. Anasthesiol Intensivmed Notfallmed Schmertzther 2000; 35(5): 285-292.

Björk M, Pettersson KJ, Österlöf G. Capillary gas chromatographic method for the simultaneous determination of local anesthetics in plasma samples. J Chromatogr Biomed Appl 1990; 553: 229-234.

Bragg CL. Interpleural analgesia. Heart Lung 1991; 20(1): 30-38.

Bucalo BD, Mirikitani EJ, Moy RL. Comparison of skin anesthetic effectof liposomal lidocaine, nonliposomal lidocaine, and EMLA using 30-min application. Dermatol Surg 1998; 24: 537-541.

Burgess P, Perl E. Cutaneous mechanoreceptors and nociceptors. In: Handbook of Sensory Physiology. Heidelberg 1973, Springer Verlag, pp 29-78.

Callesen T, Kehlet H. Postherniorrhaphy pain. Anesthesiology 1997; 87(5): 1219-30.

Campbell J, Raja S, Cohen R, Manning D, Khan A, et al. Peripheral neural mechanisms of nociception. In: Textbook of pain, Edinburgh 1989, Churchill Livingstone, pp 22-45.

Collins WF, Nulsen FE, Randt CT. Relation of peripheral fibre size and sensation in man. Arch Neurol Psychiat 1960; 3: 381-385.

Covino BG. Pharmacology of local anaesthetic agents. Br J Anaesth 1986; 58(7): 701-716.

Dahl V, Raeder JC. Non-opiod postoperative analgesia. Acta Anaesthesiol Scand 2000; 44: 1191-1203.

Dierking GW, Ostergaard E, Ostergård HT, Dahl JB. The effects of wound infiltration with bupivacaine versus saline on postopertive pain and opioid requirements after herniorraphy. Acta Anaesthesiol Scand 1994; 38: 289-292.

Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. Anesth Analg 1988; 67(5): 479-81.

af Ekenstam B, Egner B, Petersson G. Local Anaesthetics: 1.N-alkyl pyrrolidine and N-alkyl piperidine carboxylic amides. Acta Chemica Scandinavica 1957; 11: 1183-1190.

el-Dawlatly AA, al-Faqih SR. Interpleural catheter analgesia for chronic pain treatment – a case report. Middle East J Anesthesiol 1994; 12(5): 469-474.

el-Ridy MS, Khalil RM. Free versus liposome-encapsulated lignocaine hydrochloride topical applications. Pharmazie 1999; 54: 682-684.

de Jong R. Local Anesthetics, St Louis 1994, Mosby.

Fairley JW, Reynolds F. An intradermal study of the local anaesthetic and vascular effects of the isomers of mepivacaine. Br J Anaesth. 1981; 53(11): 1211-1216.

Fassoulaki A, Sarantopoulos C, Melemeni A, Hogan Q. EMLA reduces acute and chronic pain after breast surgery for cancer. Reg Anesth Pain Med 2000; 25(4): 350-355.

Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 1988; 67: 1047-1052.

Filos KS, Lehman KA. Current concepts and practice in postoperative pain management: Need for a change? Eur Surg Res 1999; 31: 97-107.

Frenette L, Boudreault D, Guay J. Interpleural analgesia improves pulmonary function after cholecystectomy. Can J Anaesth 1991; 38: 71-74.

Frenette L. The acute pain service. Crit Care Clinics 1999; 15(1): 143-150.

Freyd MJ. The Graphic rating Scale. Educ Psychol. 1923; 14: 83-102.

Frühstorfer H, Lindblom U, Schmidt WC. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976; 39: 1071-1075.

Harrison CA, Morris S, Harvey JS. Effect of ilioinguinal and iliohypogastric nerve block and wound infiltration with 0.5% bupivacaine on postoperative pain after hernia repair. Br J Anaesth 1994; 72: 691-693.

Hedenstierna G, Tokics L, Lundqvist H, Andersson T, Strandberg Å, Brismar B. Phrenic nerve stimulation during halothane anesthesia. Anesthesiology 1994; 80: 751-760.

Holloway GA, Watkins DW. Laser Doppler measurement of cutaneous blood flow. J Invest Dermatol 1977; 69: 306-309.

Holst P, Erichsen CJ, Dahl JB, Hjortsö NC, Grinsted J. Effects of lidocaine aerosol on postoperative pain and wound tenderness following minor gynecological laparotomy. Acta Anaesthesiol Scand 1992; 36: 112-114.

Honegger H, Hessler H. The discovery of local anesthesia. II. The friendship between Karl Koller and Sigmund Freud. Klin Monatsbl Augenheilkd 1970; 157(4): 569-78.

Huskisson EC, Shenfield GM, Taylor RT, Hart FD. A new look at ibuprofen. Rheumatol Phys Med. 1970; 10:Suppl 10: 88-98.

Huskisson EC. Visual analogue scales. In Pain Measurement and Assessment; New York 1983, Raven Press.

Johansson B, Hallerback B, Stubberod A, Janbu T, Edwin B, Glise H, Solhaug JH. Preoperative local infiltration with ropivacaine for postoperative pain relief after inguinal hernia repair. A randomised controlled trial. Eur J Surg. 1997; 163(5): 371-378.

Jorfeldt L, Löfström B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 1968;12:153-169.

Kaukinen S, Kaukinen L, Kataja J, Karkkainen S, Heikkinen A. Interpleural analgesia for postoperative pain relief in renal surgery patients. Scand J Urol Nephrol. 1994; 28(1): 39-43.

Keele KD. The pain chart. Lancet 1948; II: 6-8.

Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78(5): 606-17.

Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997; 78(5): 507-514.

Koller C. On the use of cocaine for producing anesthesia of the eye. Lancet 1884, 2: 990 - 992.

Kvalheim L, Reiestad F. Intrapleural catheter in the mangement of postoperative pain. Anaesthesiology 1984; 61:A231.

Lafont ND, Legros FJ, Boogaerts JG. Use of liposome-associated bupivacaine in a cancer pain syndrome. Anaesthesia 1996; 51: 578-579.

Lim R, Guzman F. In Pain, New York 1968.

Mancini G, Cabbonara AO, Heremans JF. Immunochemical quantification of antigens by singel radial immunodiffusion. Immunochemistry 1965; 2: 235-254.

Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. J Pharm Sci 1974; 63: 306-307.

McKenzie AG, Mathe S. Interpleural local anaesthesia: anatomical basis for mechanism of action. Br J Anaesth 1996; 76(2): 297-299.

McMahon S, Dimitrieva N, Koltzenburg M. Visceral pain. Br J Anaesth 1995; 75: 132-144.

Merskey H. Pain terms: A list with definitions and notes on usuage. Recommended by the IASP subcommittee on taxonomy. Pain 1979; 6: 249-252.

Morley. Vivid memory for “everyday” pains. Pain 1993; 55: 55-62.

Mulroy MF. Regional anesthetic techniques. Int Anesthesiol Clin 1994; 32(3): 81-98.

Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. Pain 1990; 41: 167-234.

Oakley MJ, Smith JS, Anderson JR, Fenton-Lee D. Randomized placebo-controlled trial of local anesthetic infusion in day-case inguinal hernia repair. Br J Surg 1998; 85: 797-799.
.
Ohnaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. Pain 1975; 1: 379-384.

Oxorn DC, Whatley GS. Post-cholecystectomy pulmonary function following interpleural bupivacaine and intramuscular pethidine. Anaesth Intensive Care 1989; 17(4): 440-443.

Perbeck L, Lundh F, Svensson L, Thulin L. Fluorescin flowmetry: A method for measuring relative capillary blood flow in the intestine. Clin Physiol 1985: 5: 281-292.

Polomano RC, Blumenthal NP, Riegler FX. Interpleural analgesia for the managements of postoperative pain. Medsurg Nurs 1993; 2(3): 185-190.

Price DP, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994; 56: 217-226.

van Raay JJAM, Roukema JA, Lenderink BW. Intraoperative wound infiltration with bupivacaine in patients undergoing elective cholecystectomy. Arch Surg 1992; 127: 457-459.

Rademaker BM, Sih IL, Kalkman CJ, Henny CP, Filedt Kok JC, Endert E, Zuurmond WW. Effects of interpleurally administered bupivacaine 0.5% on opioid analgesic requirements and endocrine response during and after cholecystectomy: a randomized double-blind controlled study. Acta Anaesthesiol Scand 1991; 35(2): 108-112.

Raja S, Meyer R, Campbell J. Peripheral mechanism of somatic pain. Anesthesiology 1988; 68: 571-590.

Ramajoli F, De Amici D. Is there a bilateral block of the thoracic sympathetic chain after unilateral intrapleural analgesia? Anesth Analg 1998; 87(2): 360-367.

Rawal N, Axelsson K, Hylander J, Allvin R, Amilon A, Lidegran G, Hallén J. Postoperative patient-controlled local anesthetic administration at home. Anesth Analg 1998; 86: 86-89.

Rawal N, Allvin R. Postoperativ smärta är ett onödigt lidande. Modell för ”akutsmärtservice” implementerad i Örebro. Läkartidningen 2001; 98(14): 1648-1654.

Reiestad F, McIlvaine WB, Barnes M, Kvalheim L, Haraldstad P, Pettersen B. Interpleural analgesia in the treatment of severe thoracic postherpetic neuralgia. Reg Anesth 1990; 15(3): 113-117.

Reiestad F, McIlvaine WB, Kvalheim L, Stokke T, Pettersen B. Interpleural analgesia in treatment of upper extremity reflex sympathetic dystrophy. Anesth Analg. 1989 ;69(5): 671-673.

Reiestad F, Strömskag KE. Intrapleural catheter in the management of postoperative pain: a preliminary report. Reg Anesth 1986; 11:89-91.

Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for avaluating pain. Anesthesia 1976; 31:1191-1198.

Reynolds F, Aps C. Antiarrythmic action of lignocaine in early myocardial infarction. Lancet 1977; 1(8023): 1202.

Rosenberg J, Kehlet H. Does affective postoperative pain management influence surgical morbidity? Eur Surg Res 1999; 31: 133-137.

Russel WC, Ramsay H, Fletcher DR. The effect of incisional infiltration of bupivacaine upon pain and respiratory function following open cholecystectomy. Aust N.Z. J Surg 1993; 63: 756-759.

Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989; 69: 563-569.

Scott J, Huskison E. Graphic representation of pain. Pain 1976; 2: 175-184.

Scott N, Mogensen T, Greulich A, Hjortsö N, Kehlet H. No effect of continous i.p. infusion of bupivacaine on postoperative analgesia, pulmonary function and the stress response to surgery. Br J Anaesth 1988; 61: 165-168.

Seltzer JL, Larijani GE, Goldberg ME, Marr AT. Intrapleural bupivacaine - a kinetic and dynamic evaluation. Anesthesiology 1987 ; 67(5): 798-800.

Sihota MK, Holmblad BR. Horner´s syndrome after intrapleural anesthesia with bupivacaine for postherpetic neuralgia. Acta Anaesthesiol Scand 1988; 32(7): 593-594.

Sinatra RS. Current methods of controlling post-operative pain. Yale J Biol Med 1991; 64(4):351-374.

Sinclair R, Westlander G, Cassuto J, Hedner T.Postoperative pain relief by topical lidocaine in the surgical wound of hysterectomized patients. Acta Anaesthesiol Scand. 1996;40(5): 589-594.

Sinclair R, Cassuto J, Hogstrom S, Linden I, Faxen A, Hedner T, Ekman R. Topical anesthesia with lidocaine aerosol in the control of postoperative pain. Anesthesiology. 1988; 68(6): 895-901.

Strömskag KE, Hauge O, Steen PA. Distribution of local anesthetics injected into the interpleural space, studied by computerized tomography. Acta Anaesthesiol Scand 1990; 34(4): 323-326.

Strömskag KE, Mino BG, Lindeberg A. Comparison of 40 ml of 0.25% intrapleural bupivacaine with epinephrine with 20 ml of 0.5% intrapleural bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1991; 73(4): 397-400.

Taenzer P, Melzack R, Jeans M. Influence of psychological factors on postoperative pain, mood and analgesic requirements. Pain 1986; 24: 331-342.

Tverskoy M, Cozacov C, Ayache M, Bradley EL Jr, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg. 1990; 70(1): 29-35.

Tucker GT. Is plasma binding of local anesthetics important? Acta Anesth Belg 1988; 39: 147-150.

Wallin G, Cassuto J, Högström S, Hedner T. Influence of intraperitoneal anaesthesia on pain and the sympathoadrenal response to abdominal surgery. Acta Anaesthesiol Scand 1988; 32: 553-558.

Wildsmith JAW, Brown DT, Paul D, Johnson S. Structure-activity relationships in differential nerve block at high and low frequency stimulation. Br J Anaesth 1989; 63: 444-452.

Yaksh TL, Hammond DL. Peripheral and central substances involved in the rostrad transmission of nociceptive information. Pain 1982; 13: 1-85.

Zieren J, Zieren HU, Jacobi CA, Müller JM. Repeated boluses of local anesthetic for pain relief after inguinal hernia repair. Eur J Surg 1999; 165: 460-464.

Åberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. Acta Pharmacologica et Toxicologica 1972; 31: 273-286.

Åkerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent opivacaine (LEA 103). Acta Anaesthesiol Scand 1988; 32: 571-578.

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