DEPARTMENT OF ANAESTHESIA AND INTENSIVE CARE MEDICINE
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FINLAND

CLINICAL STUDIES ON EPIDURAL AND SPINAL POSTOPERATIVE ANALGESIA

WITH SPECIAL REFERENCE TO CONTINUOUS TECHNIQUES OF ADMINISTRATION AND ADJUVANT DRUGS

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Academic Dissertation

To be presented, with the permission of the Medical Faculty of the University of Helsinki, for public examination in Auditorium II, Biomedicum Helsinki, Haartmaninkatu 8, 00290 Helsinki, on March, 15th, 2008, at 10 a.m.

Helsinki 2008

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ISBN 978-952-92-3386-1 (paperback)

ISBN 978-952-10-4543-1 (PDF)

http://ethesis.helsinki.fi

Layout Johannes Förster and Jari Simonen (Lifeteam Finland)

Helsinki University Printing House

Helsinki 2008

Dedicated to my patients who took part in this thesis

Apollo's Chariot

Odilon Redon (*c*. 1905-1916)

"… the joy of full daylight,
in contrast to the sadness of night and shadows,
like the happiness of feeling better after great pain."

Odilon Redon (1840-1916)

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Abstract

Background and Aims: Continuous epidural analgesia (CEA) and continuous spinal postoperative analgesia (CSPA) provided by a mixture of a local anaesthetic and an opioid are widely used for pain control after major surgery. These techniques, however, may be associated with dose-dependent side-effects as hypotension, weakness in the legs, respiratory depression, and nausea and vomiting. At times, they may fail to offer sufficient analgesia, *e.g.*, because of a misplaced catheter. The correct position of an epidural catheter might be confirmed during CEA by the supposedly easy and reliable epidural stimulation test (EST) (electrical neurostimulation). In the past years, CSPA found its way with the introduction of what is referred to as microcatheters, particularly in orthopaedic surgery. The aims of this thesis were to determine a) whether the efficacy, tolerability, and reliability of CEA might be improved by adding the α_2-adrenergic agonists adrenaline (epinephrine) and clonidine to CEA, and by the repeated use of EST during CEA; and, b) the feasibility of CSPA given through a microcatheter after vascular surgery of the lower extremities.

Patients and Methods: Studies I–IV were double-blinded, randomized, and controlled trials; Study V was of a diagnostic, prospective nature. Patients underwent arterial bypass surgery of the legs in Studies I (n=50) and IV (n=46), total knee arthroplasty in Studies II (n=70) and III (n=72), and abdominal surgery or thoracotomy in Study V (n=30). In Studies I–III, postoperative lumbar CEA consisted of regular mixtures of low-dose ropivacaine and fentanyl either without or with adrenaline (2 µg/ml in Study I and 4 µg/ml in Study II) and clonidine 2 µg/ml (Study III). In Study IV, CSPA was given through a microcatheter (28G) and contained either ropivacaine (max. 2 mg/h) or a mixture of ropivacaine (max. 1 mg/h) and morphine (max. 8 µg/h). In Study V, epidural catheter tip position was evaluated both by EST at the moment of catheter placement and several times during CEA, and by epidurography as reference diagnostic test. CEA and CSPA were administered for 24 h (III and IV) or 48 h (I, II, and V). Study parameters included pain scores assessed with a visual analogue scale, requirements of rescue pain medication, vital signs, and side-effects.

Results: Adrenaline (I and II) had no beneficial influence as regards the efficacy or tolerability of CEA. The total amounts of epidurally-infused drugs were even increased in the adrenaline group in Study II (p=0.02, RM ANOVA; mean inter-group difference 40 ml (95% CI 5–75 ml)). Clonidine (III) augmented pain relief with lowered amounts of epidurally infused drugs (p=0.01, RM ANOVA; mean inter-group difference 13 ml (95% CI 4–22 ml)) and reduced need for rescue oxycodone given i.m. (p=0.027, MW-U; median difference in oxycodone consumption 3 mg (95% CI 0–7 mg)). Clonidine did not contribute to sedation and its influence on haemodynamics was minimal. CSPA (IV) provided satisfactory pain relief with only limited blockade of the legs (no inter-group differences between the combination of low-dose ropivacaine and morphine compared to the higher ropivacaine concentration alone). EST (V) was often related to technical problems and difficulties of interpretation (*e.g.*, need to flush the catheter with saline; influence of respiratory activity; EST failed to identify the four patients whose catheters were outside the spinal canal already at the time of catheter placement).

Conclusions: As adjuvants to lumbar CEA, clonidine only slightly improved pain relief, while adrenaline did not provide any benefit. The role of EST applied at the time of epidural catheter placement or repeatedly during CEA remains open. The microcatheter CSPA technique appeared effective and reliable, but needs to be compared to CEA, the analgesia technique frequently used after peripheral arterial bypass surgery.

Abbreviations

95% CI	95% confidence intervals
ABPI	Ankle-brachial blood pressure index
ASA class	American Society of Anesthesiologists physical status classification
BMI	Body mass index
χ^2 test	Chi-square test
CEA	Continuous epidural analgesia
CSA	Continuous spinal anaesthesia
CSF	Cerebrospinal fluid
CSPA	Continuous spinal postoperative analgesia
CVP	Central venous pressure
Day 0, 1, and 2	Day of surgery as well as first and second postoperative day, respectively
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetate
EST	Epidural stimulation test
F	*F*-ratio
G	Gauge, a measure to indicate the diameter of needles and catheters
GA	General anaesthesia
i.m.	Intramuscular
i.v.	Intravenous
LEA	Lumbar epidural analgesia
LMWH	Low-molecular weight heparin
LOR	Loss-of-resistance
MAP	Mean arterial pressure
max.	Maximum
MW-*U*	Mann-Whitney *U* test
No., no., *n*	Number
NA	Not assessed or not applicable
NSAID	Non-steroidal anti-inflammatory drug
p	*p*-value, probability
PACU	Postanaesthesia care unit
PCA	Patient controlled analgesia
p.o.	Per os
PDPH	Postdural puncture headache
PHH-score	Prince Henry Hospital pain score
PONV	Postoperative nausea and vomiting
RCT	Randomized controlled trial
RM ANOVA	Repeated-measurement analysis of variance
s.c.	Subcutaneous
SD	Standard deviation
SpO_2	Oxygen saturation measured by pulse oximetry
SSA	Single-dose spinal anaesthesia
TEA	Thoracic epidural analgesia
TKA	Total knee arthroplasty
VAS	Visual analogue scale

List of Original Publications

This thesis is based on the following original studies which are referred to in the text by their Roman numerals (I–V).

I Förster JG, Niemi TT, Aromaa U, Neuvonen PJ, Seppälä TA, Rosenberg PH. Epinephrine added to a lumbar epidural infusion of a small-dose ropivacaine-fentanyl mixture after arterial bypass surgery of the lower extremities. Acta Anaesthesiol Scand 2003; 47: 1106-1113

II Förster JG, Lumme HM, Palkama VJ, Rosenberg PH, Pitkänen MT. Epinephrine 4 µg/mL added to a low-dose mixture of ropivacaine and fentanyl for lumbar epidural analgesia after total knee arthroplasty. Anest Analg 2008; 106: 301-304

III Förster JG, Rosenberg PH. Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. Br J Anaesth 2004; 93: 670-677

IV Förster JG, Rosenberg PH, Niemi TT. Continuous spinal microcatheter (28 gauge) technique for arterial bypass surgery of the lower extremities and comparison of ropivacaine with or without morphine for postoperative analgesia. Br J Anaesth 2006; 97: 393-400

V Förster JG, Niemi TT, Salmenperä MT, Ikonen S, Rosenberg PH. Evaluation of the epidural catheter position by epidural nerve stimulation in conjunction with continuous epidural analgesia in adult surgical patients; *submitted*

Introduction

Epidural and intrathecal routes, also known as neuraxial routes, for the administration of drugs are used for the treatment of pain after surgery. This is in analogy to epidural and spinal anaesthesia during surgery where local anaesthetics are given close to the 'target organ', namely the spinal cord and nerve roots. Its aim is to deliver minimal yet effective drug doses with limited side-effects.

The continuous epidural analgesia (CEA) technique has been used to offer analgesia following various surgical procedures. In a meta-analysis, Block et al. described epidural analgesia as providing better postoperative analgesia when compared to parenteral opioids [Block *et al.* 2003].

Epidural analgesia, however, does not always grant adequate pain relief. Of patients given postoperative epidural analgesia, 21% complained of moderate-severe pain while another 8% described their pain as being severe [Dolin *et al.* 2002]. Despite the many advances in pain management, postoperative pain remains an important cause of suffering [Apfelbaum *et al.* 2003].

In the neuraxial techniques, where local anaesthetics and opioids are often combined [Walker *et al.* 2002], the provision of effective analgesia may be limited because of side-effects. Possible undesired effects associated with local anaesthetics are hypotension and weakness of the legs [Block *et al.* 2003]; when opioids are used, nausea and itching may result, as might depression of respiration [Breivik 1992; Block *et al.* 2003]. The frequency and grade of these side-effects are, to a large degree, dose-dependent. Therefore, in an attempt to lower the dosages, one may add other antinociceptive substances from different pharmacological classes to the mixture of the local anaesthetic and opioid. Such drug combinations may produce analgesia by additive or even synergistic ('supra-additive') mechanisms and permit smaller doses of each drug with correspondingly fewer dose-related side-effects.

The list of adjuvant drugs studied in regional anaesthesia in recent years includes the α_2-adrenergic agonists adrenaline (epinephrine) and clonidine. Concerning α_2-adrenergic agonists, Gordh stated [Gordh 1992] that treatment with clonidine and other α_2-adrenoceptor agonists may represent an important new approach to neuraxial analgesia by carrying a lower risk of respiratory depression.

Adrenaline has been employed as an adjuvant in regional anaesthesia for more than a century. The activity of adrenaline given epidurally is presumably due to its vasoconstrictive effect; local blood flow is decreased resulting in a slower rate of absorption and prolonging the effect of co-administered drugs. Additionally, adrenaline possesses its own pharmacodynamic analgesic effect which is expressed through α_2-adrenoreceptors in the dorsal horn of the spinal cord [Reddy *et al.* 1980]. Adrenaline added to an infusion of an opioid and a local anaesthetic may be useful in improving thoracic CEA [Niemi and Breivik 1998] but its value in lumbar CEA remains contradictory [Curatolo 2002].

Clonidine has been used as an adjuvant in connection with various regional anaesthesia techniques [Eisenach *et al.* 1996] including postoperative epidural analgesia [Armand *et al.* 1998]: In many studies, clonidine was combined with either a local anaesthetic or an opioid; however, there are only a limited number of studies in which clonidine was added to an epidural infusion containing both a local anaesthetic and an opioid.

Regardless of which drug or drugs are given through an epidural catheter, analgesia will be inadequate if the tip of the catheter is not properly placed within the epidural space. The

identification of the epidural space using the routine loss-of-resistance technique [Bromage 1954; Bonica 1956] and the positioning of the epidural catheter largely rely on the feel and the dexterity of the anaesthetist but without visual control of the catheter position. Although the catheter may initially lie correctly within the epidural space, subsequently it may migrate to a less suitable level or even slip out of the epidural space. In one report, this incidence of premature catheter dislodgement was about 6% [Dolin *et al.* 2002].

A potentially simple technique to confirm the position of the epidural catheter was described by Tsui and colleagues. They judged the location of the catheter to be correct on the basis of truncal or limb movement using electrical neurostimulation applied through the catheter (epidural stimulation test (EST)) [Tsui *et al.* 1998]. As yet, there are no reports of EST being used both for the placing of the catheter and later during CEA. The repetition of EST would be particularly interesting in cases where at first a CEA was functioning well but later would fail to yield adequate analgesia; hence, one would suspect that the catheter tip no longer lies within the epidural space.

Finally, continuous spinal anaesthesia (CSA) has received increasing attention [Denny and Selander 1998] with the introduction of small calibre spinal catheters (so-called microcatheters). CSA enables incremental doses of the local anaesthetic to be injected, thus providing for spinal anaesthesia of an adequate degree and duration that is suitable also for prolonged surgery. After CSA, the spinal catheter can be utilized to administer continuous spinal postoperative analgesia (CSPA). Spinal catheters have been used for CSPA with good results mainly in orthopaedic patients [Denny and Selander 1998].

The clinical studies carried out here focused on measures to deliver effective, well-tolerated, and good-quality continuous neuraxial postoperative analgesia:

a) the α_2-adrenergic agonists adrenaline and clonidine that were used as adjuvants to CEA administered at a lumbar level after arterial bypass surgery of the legs or total knee arthroplasty;
b) the confirmation of the epidural catheter position by EST in conjunction with CEA in patients scheduled for major abdominal surgery or thoracotomy; and
c) CSPA administered through a microcatheter after arterial bypass surgery of the lower extremities.

Review of the Literature

Need for effective postoperative analgesia

Postoperative pain treatment should be an integral component of the routine surgical and anaesthetic management not only for humanitarian reasons [Cousins *et al.* 2004] but also because it can help to reduce morbidity and complications as well as accelerate rehabilitation [Kehlet 1999]. For example, resolute pulmonary and physical rehabilitation are crucial to prevent potential pulmonary complications especially after thoracotomy and major abdominal procedures. Rehabilitation, however, may be hindered by inadequate postoperative analgesia [Crews and Bridenbaugh 1995]. In another reference, severe pain after total knee arthroplasty (TKA) can delay the early commencement of physiotherapy which can have negative effects on rehabilitation being successful [Capdevila *et al.* 1999]. Furthermore, surgery stimulates a complex stress response characterised by endocrine and metabolic changes in addition to inflammatory and immunosuppressive consequences. This stress reaction can increase morbidity and mortality from myocardial ischaemia, thromboembolic events, and infections. Good postoperative analgesia is an important avenue to attenuate the surgical stress response [Kehlet and Dahl 2003]. This appears particularly vital in patients whose organ functions are already impaired preoperatively. For example, patients with generalized arteriosclerosis presenting for artery repair surgery often are elderly and have various co-existing diseases.

Furthermore, the association between tissue damage of surgery, severity of acute postoperative pain and persistent postoperative pain is well known [Perkins and Kehlet 2000]. Tissue damage caused by surgery can initiate pathophysiological processes in the peripheral and central nervous system that may lead to chronicity [Cousins *et al.* 2000]. For instance, persistent pain after arthroplasty is a known problem; in a prospective observational study more than 18% of patients reported moderate to severe pain at six months and 13% at one year following TKA [Brander *et al.* 2003].

Regardless of the many advances in pain management, acute postoperative pain remains an important cause of considerable suffering [Dolin *et al.* 2002; Apfelbaum *et al.* 2003]. The overall mean (95% CI) incidence of moderate-severe and severe postoperative pain was almost 30% (26%–33%) and 11% (8%–13%), respectively, in pooled data from about 20 000 patients treated with intramuscular opioid, patient controlled analgesia (PCA), or epidural analgesia [Dolin *et al.* 2002].

Spinal and epidural anaesthesia (neuraxial anaesthesia)

Spinal and epidural anaesthesia refer to the administration of a local anaesthetic into the intrathecal and epidural space, respectively. The origin of these central or neuraxial anaesthesia techniques began more than a century ago. Since then, neuraxial anaesthesia has undergone many developmental changes both in drugs and equipment, such as, the popularization of the loss-of-resistance (LOR) technique to identify the epidural space [Dogliotti 1933] and the continuous intrathecal technique *via* an indwelling catheter [Tuohy 1944].

Today, spinal and epidural anaesthesia are used for a wide variety of surgical procedures including orthopaedic and vascular surgery of the lower limbs, and gynaecological and obstetrical surgery. Debate continues as to whether regional anaesthesia results in less postoperative morbidity

and mortality than does general anaesthesia (GA). A meta-analysis of over 140 trials where surgery was performed either under GA alone or under neuraxial block with or without GA indicated that central neuraxial blockade reduced cardiac, pulmonary, and thromboembolic morbidity and mortality by 30%–50% in patients who had undergone lower-body surgery [Rodgers *et al.* 2000]. A Cochrane Systematic Review of GA *versus* neuraxial anaesthesia in adults for hip surgery showed a reduced risk of deep vein thrombosis and one month mortality in favour of neuraxial anaesthesia [Urwin *et al.* 2000]. Other randomized studies including many hundreds of patients each, found little subgroup advantage or no benefit in favour of neuraxial anaesthesia with regard to mortality or major complications [Bode *et al.* 1996; Park *et al.* 2001; Norris *et al.* 2001; Rigg *et al.* 2002; Peyton *et al.* 2003]. Various possible explanations for this discrepancy include the wide variety of possible techniques (which regional technique should be compared to which combination of general anaesthetic drugs), the use of heterogeneous patient populations, and the including of older studies in the comparison (because overall improvement in perioperative care has favourably affected prognosis and would thus affect the data) [Wildsmith 2003; De Leon-Casasola 2003]. In any case, Wildsmith feels that postoperative analgesia is of better quality when regional anaesthesia is employed [Wildsmith 2003].

From single-dose to continuous neuraxial anaesthesia and analgesia

Earlier, only short-acting local anaesthetics such as cocaine and procaine were available and therefore the duration of the single-dose neuraxial anaesthesia was insufficient for longer lasting procedures. This situation was improved by the arrival of longer acting local anaesthetics, *e.g.*, bupivacaine. Other attempts to provide prolonged neuraxial anaesthesia included the addition of other drugs to the local anaesthetic (*e.g.*, vasoconstrictors [Pitkin 1940]), the development of sustained release preparations (*e.g.*, [Paavola *et al.* 1998]), and, last but not least, repeated or continuous intrathecal and epidural administration of drugs (regarding the latter, see Table 1).

Table 1. Main stages in development of continuous neuraxial anaesthesia (modified from [Brill et al. 2003]).

Year	*Comment*
1907	Concept to top-up spinal anaesthesia through spinal needle left in place after puncture by Dean
1931	Introduction of continuous (fractional doses) epidural (caudal) block in obstetrics by Aburel
1940	CSA by use of indwelling malleable needle and special split mattress by Lemmon
1942	Epidural (caudal) block by catheter in obstetrics independently described by Manalan and by Edwards and Hingson
1944	CSA by means of urethral catheter by Tuohy
1990	Introduction of microcatheters for CSA by Hurley and Lambert

CSA=Continuous spinal anaesthesia.

The concept of continuous spinal anaesthesia (CSA) was first considered in 1907 with the intention to administer top-ups of local anaesthetic during surgery through the spinal needle left in place after lumbar puncture. This technique carried considerable risks since the needle could easily cause direct damage to the surrounding tissues. The first continuous epidural (caudal) anaesthesia using a catheter was portrayed in 1942 (Table 1). In 1944, the first catheter technique for CSA was described with a No. 4 urethral catheter inserted through a 15G needle [Tuohy 1944]. However, fears that CSA would result in high incidences of postdural puncture headache (PDPH), as well as reports of low success rates [Dripps 1950] led to its decline. The use of CSA was further reduced by the expansion of the epidural catheter technique [Bromage 1954]. In 1990, the CSA technique

experienced a renaissance with the introduction of thinner catheters called ‘microcatheters’. [Hurley and Lambert 1990] (Table 1). With such fine catheters (as thin as 32G), it was believed that the incidence of PDPH would be lessened. However, the enthusiasm over CSA administered through microcatheters was dampened by reports of cauda equina syndrome [Rigler *et al.* 1991]. In the meanwhile, based on further clinical and experimental evaluation, it was reasonably argued that the problem with the cauda equina syndrome was not related *per se* to the microcatheter technique but rather to the direct neurotoxic effect of large doses of hyperbaric local anaesthetic [Rigler and Drasner 1991; Denny and Selander 1998].

Despite the setbacks and technical problems experienced, continuous neuraxial anaesthesia remains a useful tool for selected patients [Denny and Selander 1998; Rodgers *et al.* 2000; Michaloudis *et al.* 2000; Groeben 2006]. In addition, the catheter which is already in place can be utilized for epidural or spinal analgesia after surgery.

Continuous spinal anaesthesia (CSA)

Tuohy (Table 1) wrote with respect to the benefits of prolonged access to the intrathecal space [Tuohy 1944]: “The advantage of the serial or fractional doses should be axiomatic since the anesthetic agent may be added as it is needed and the necessity of administering a large or relatively large amount at one time, the so-called single dose method, is eliminated.” This implies that CSA offers two major advantages over single-dose spinal anaesthesia (SSA). Firstly, it is possible to attain anaesthesia of an adequate level and suitable (prolonged, if necessary) duration. Secondly, by titrating the local anaesthetic, it facilitates the regulation of the spread of the block and thus reduces the risk of abrupt cardiovascular depression compared with SSA.

CSA offered haemodynamic stability [Morrison *et al.* 1991; Labaille *et al.* 1992; Mahisekar *et al.* 1991] and improved haemodynamic control as compared to SSA and epidural anaesthesia [Sutter *et al.* 1989; Klimscha *et al.* 1993; Favarel-Garrigues *et al.* 1996; Casati *et al.* 1996; Holst *et al.* 1997; Maurer *et al.* 2003]. But, in contrast, there are other reports with less consistent differences regarding haemodynamic parameters when comparing CSA to SSA [Pitkänen *et al.* 1992a; Bevacqua 1993; Lundorff *et al.* 1999; Sabaté *et al.* 1994].

An intrathecal catheter allows the provision of regional anaesthesia and analgesia in situations when SSA and epidural anaesthesia would not generally be recommended (aortic stenosis, hypertrophic cardiomyopathy) or when the identification of the epidural space might be difficult (severe obesity, extremity of age) [Michaloudis *et al.* 2000]. Many anaesthetists prefer CSA for surgery of long duration and in elderly patients with a complex medical history [Denny and Selander 1998]. Prolonged surgery and co-existing diseases such as hypertension, ischaemic heart disease, diabetes mellitus, and chronic obstructive pulmonary disease are features often encountered in patients scheduled for peripheral arterial bypass surgery [Ellis *et al.* 1995].

The CSA technique must be very meticulously carried out because, “while spinal anaesthesia is not necessarily more dangerous than epidural anaesthesia, the subarachnoid space is markedly less forgiving of mistakes than the epidural space” [Bevacqua 2003].

Continuous neuraxial analgesia

In the anaesthetic literature, the abbreviation CSA is commonly used to describe the continuous administration of spinal *anaesthesia* for the *duration of surgery*. Some authors, however, use this abbreviation for continuous spinal analgesia given after surgery. In order to better distinguish between these two entities here, the acronym CSPA is employed when referring to continuous spinal *postoperative analgesia*. The shortened form CEA indicates continuous epidural analgesia

given postoperatively. The abbreviations LEA and TEA differentiate between *lumbar* and *thoracic* epidural analgesia, respectively.

The epidural and spinal routes for the administration of drugs are often used for the treatment of acute perioperative as well as chronic pain. This is in analogy to epidural and spinal anaesthesia where local anaesthetics are given close to the spinal cord and nerve roots with the aim to apply minimal yet effective drug doses with only limited side-effects.

Continuous spinal postoperative analgesia (CSPA)

The history of postoperative pain relief utilizing CSPA began more than half a century ago [Ansbro *et al.* 1952]. Following the introduction of thinner catheters two decades ago, the technique has been revived [Hurley and Lambert 1990; Denny and Selander 1998].

CSPA has been used with good results particularly in orthopaedic patients [Standl *et al.* 1995a; Niemi *et al.* 1996; Bachmann *et al.* 1997; Möllmann *et al.* 1999; Maurer *et al.* 2003; Gurlit *et al.* 2004]. In some studies, however, complicating factors of recurring motor blockade have surfaced during CSPA with bupivacaine [Niemi *et al.* 1996; Bachmann *et al.* 1997]. For this reason, CSPA with ropivacaine might be advantageous with regard to the incidence and degree of motor blockade [McClure 1996].

There are also promising reports describing patient-controlled CSPA after orthopaedic surgery [Rundshagen *et al.* 1997; Vercauteren *et al.* 1998; Rundshagen *et al.* 1998].

Continuous epidural analgesia (CEA)

CEA has been used for postoperative analgesia for many decades. The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine lately described CEA as follows [ANZCA 2005, page 110]: "Epidural analgesia … has become a widely used technique for the management of acute pain in adults and children, particularly after surgery and sometimes trauma, and in parturients." The universal efficacy of CEA as a pain relieving method is well documented. In a meta-analysis [Block *et al.* 2003], epidural analgesia provided better postoperative analgesia when compared with parenteral opioids. CEA when compared to parenteral opioids given either intravenously by PCA or intramuscularly resulted in a significant lower incidence of moderate-severe pain (21% *versus* 36% and 67%, respectively) and severe pain (8% *versus* 10% and 29%, respectively) [Dolin *et al.* 2002]. Superior pain relief was noted with CEA in contrast to other measures after intra-abdominal aortic, gastric, biliary, or colon operations [Park *et al.* 2001], after major abdominal surgery in high-risk patients [Rigg *et al.* 2002], after intra-abdominal surgery [Werawatganon and Charuluxanun 2005], after coronary artery bypass surgery [Liu *et al.* 2004], and after TKA [Choi *et al.* 2003; Farag *et al.* 2005].

Whether CEA as a single intervention has beneficial effects on morbidity and mortality remains a matter of debate, probably because the complex perioperative care has not been adjusted sufficiently in past analyses [Kehlet and Dahl 2003]. Moreover, it is difficult to summarize the available data related to its efficacy because CEA is not a standardized entity but can be supplied by various pharmacological drugs, given at different levels of the epidural space, and for a wide range of procedures [De Leon-Casasola 2003]. Nevertheless, there is abundant data suggesting that CEA can reduce morbidity with respect to several organ systems (Table 2). For example, CEA supported early rehabilitation and functional outcome after TKA and reduced the incidence of graft occlusion after peripheral vascular surgery (Table 2).

Table 2. Potential benefits of continuous epidural analgesia on postoperative morbidity and mortality.

Organ system or outcome parameter	*Potential beneficial effect*
Myocardium	Reduction in postoperative myocardial infarction with TEA [Beattie *et al.* 2001; Beattie *et al.* 2003]
	Reduced cardiac dysrhythmias [Liu *et al.* 2004; Guay 2006a]
Respiratory system	Improved oxygenation of blood and reduction in pulmonary complications, *e.g.*, pulmonary infections [Ballantyne *et al.* 1998]
	Reduced respiratory failure [Rigg *et al.* 2002] and pulmonary complications [Liu *et al.* 2004]
	Earlier extubation [Liu *et al.* 2004; Groeben 2006; Guay 2006a]
Gastrointestinal system	Reduced gastrointestinal paralysis compared with opioid-based analgesia after abdominal surgery [Jørgensen *et al.* 2000]
Stress response	Reduction of sympathoadrenergic stress response after thoracotomy [Salomäki *et al.* 1993] and TKA [Adams *et al.* 2002]
Rehabilitation	Better knee flexion, faster ambulation, and shorter hospital stay after TKA [Singelyn *et al.* 1998]
	Improved early rehabilitation after TKA [Farag *et al.* 2005]
Graft performance after vascular surgery	Lower incidence of re-operation for inadequate tissue perfusion [Christopherson *et al.* 1993]
	Decreased risk of arterial thrombotic complications [Rosenfeld *et al.* 1993]
	Reduced incidence of graft occlusion and improved graft blood flow [Perler *et al.* 1995]

TEA=Thoracic epidural analgesia. TKA=total knee arthroplasty.

CEA is a safe and practical method for pain treatment in the usual postsurgical ward setting with few complications provided that patients are under strict regular surveillance by trained staff [Salomäki *et al.* 1996; Rygnestad *et al.* 1997; Wheatley *et al.* 2001]. This also applies to patient-controlled epidural analgesia which has become increasingly popular over the past years [Vercauteren *et al.* 1995; Liu *et al.* 1998; Silvasti and Pitkänen 2001; Standl *et al.* 2003].

As an interim summary, CEA with a low-dose combination of a local anaesthetic and opioid is recommended for pain treatment in major surgery [Kehlet and Dahl 2003]. Nevertheless, it cannot always provide sufficient pain relief: The incidence of moderate to severe pain was 21% and that of severe pain reached almost 8% in a recent review [Dolin *et al.* 2002]. One concept to improve neuraxial analgesia is to use additional compound drugs or 'adjuvants'.

Adjuvants

Adjuvants in neuraxial analgesia – general aspects

Adjuvants are substances which by themselves possess low potency or in higher doses display undesirable side-effects but allow for a reduction of doses of other co-administered active compounds. The combination thus may allow for reduced doses of each drug accompanied with fewer dose-related side-effects. The component drugs from various pharmacological classes can produce a desired effect by additive or even synergistic ('supra-additive') mechanisms. This idea has important implications in any therapeutic area in which additive and synergistic combinations may be utilized to develop the potency, efficacy, or therapeutic window associated with the treatment regimen. Synergy-enabled decreases in the dose may prove advantageous in clinical pain management as, for example, in chronic, opioid-resistant pain [Coombs *et al.* 1986]. However, when investigating adjuvants for potential benefits, one must keep in mind that combining several drugs might unexpectedly result in antagonistic ('sub-additive') interactions.

In the 1970s, the discovery of opioid receptors in the brain [Goldstein *et al.* 1971; Pert and Snyder 1973] and spinal cord tissues [LaMotte *et al.* 1976] offered new possibilities for central neuraxial analgesia [Yaksh and Rudy 1976]. Originally, it was thought that opioids applied through the neuraxis might be as effective as when given systematically albeit in lower doses and thus having a reduced risk of respiratory depression. Therefore, much was expected from this new mode of pain treatment which is virtually devoid of effects on the motor function or sensory modalities. However, over the years it was concluded that neuraxial opioids are not free from meaningful side-effects (*e.g.*, respiratory depression) and alone do not solve all problems of pain.

Nowadays, local anaesthetics and opioids are often combined for central neuraxial analgesia with plenty of basic pharmacologic and clinical evidence that pain management can be improved in this manner [Breivik 1992; Solomon and Gebhart 1994; Vercauteren and Meert 1997; Walker *et al.* 2002]. Opioids play such an integral role in most regional anaesthetic techniques that many authors regard them as routine rather than adjuvant compounds.

With the epidural and intrathecal route of administration, achieving effective analgesia may be restricted due to adverse effects. Local anaesthetics may cause hypotension and weakness of the legs [Block *et al.* 2003; Bachmann *et al.* 1997], while opioids may result in nausea, itching, and the depressed breathing [Breivik 1992; Block *et al.* 2003]. The frequency and degree of such side-effects are for the most part dose-dependent.

α_2-Adrenergic agonists – general aspects

Important adjuvants for regional anaesthesia include the α_2-adrenergic agonists adrenaline (epinephrine) and clonidine. The interest in α_2-adrenoceptor agonists has increased during the last two decades. In 1992, Gordh noted [Gordh 1992] that such compounds may offer a new approach to neuraxial analgesia with a decreased risk of respiratory depression [Penon *et al.* 1991].

Agonists of α_2-adrenergic receptors provide dose-dependent pain relief by an opioid-independent mechanism [Yaksh and Reddy 1981]. They produce antinociception by stimulating the postsynaptic α_2-adrenergic receptors in the dorsal horn of the spinal cord. This mimics the effect of noradrenaline which is released from descending inhibitory pathways in the central nervous system. Thus, a decreased activity of second-order neurons and wide dynamic range neurons in the dorsal horn occurs [Reddy *et al.* 1980; Yaksh and Reddy 1981; Collins *et al.* 1984; Murata *et al.* 1989] which, in turn, attenuates the input from peripheral nociceptive Aδ and C fibres. The analgesic effect transmitted through α_2-adrenergic receptors is reversed by the α-receptor antagonist phentolamine, although it remains unaffected by the β-receptor antagonist propranolol or the opioid antagonist naloxone [Reddy *et al.* 1980; Yaksh and Reddy 1981].

Functional interactions between μ-opioid receptors and α_2-adrenergic receptors have been described. They share a common signalling system mediated through inhibitory G-proteins whose activation results in increased potassium conductance and cell membrane hyperpolarisation in the Locus coeruleus of the brain stem [Aghajanian and Wang 1987]. Synergistic effects between μ-opioid receptors and α_2-adrenergic receptors are found at the spinal level *in vivo* [Meert and De Kock 1994; Stone *et al.* 1997]. Interactions between α_2-adrenergic agonist and local anaesthetics have also been proposed, *e.g.*, the potentiation of the effect of lidocaine by clonidine [Gaumann *et al.* 1992; Hao *et al.* 2001].

Adrenaline

For more than a century, adrenaline (epinephrine) has been utilized as an adjuvant in regional anaesthesia [Weber 1904]. This has been done in order to reduce plasma concentrations of co-administered drugs and to enhance their anaesthetic action [Covino and Wildsmith 1998; Burm *et*

al. 1986]. This action is primarily due to adrenaline's vasoconstrictive properties: By decreasing the local blood flow the absorption of co-administered local anaesthetics and opioids is delayed which, in turn, intensifies and prolongs the actions of the compounds [Covino and Wildsmith 1998; Bernards and Kopacz 1999]. A second possible mechanism of (peripheral) block improvement by adrenaline is described in a proposed two-compartment model, having an outer compartment (including epineurial tissue) and an inner 'effector' compartment (including endoneurium and nerve fibres) [Sinnott *et al.* 2003]: The observation that similar intraneural lidocaine contents produced varying degrees of analgesia (with intensified analgesia in the presence of adrenaline) might be because adrenaline facilitated the uptake of the local anaesthetic into the effector compartment [Sinnott *et al.* 2003]. The antinociceptive capability of neuraxial adrenaline communicated through α_2-adrenoreceptors [Reddy *et al.* 1980; Collins *et al.* 1984] was seen in humans both for intrathecal [Priddle and Andros 1950] and lumbar epidural administration [Curatolo *et al.* 1997].

Adrenaline 200–500 µg (single-dose) added to different spinal local anaesthetics gave varying results with respect to the prolongation of the block depending upon the dose of adrenaline and the local anaesthetic used. The addition, for example, of adrenaline 200 µg to an intrathecal dose of 7.5 mg bupivacaine prolonged sensory modalities, duration of motor blockade, and the time to void by about 30–50 min [Moore *et al.* 1998]. Thus, adrenaline may extend surgical anaesthesia for ambulatory surgery but, at the same time, delay the time until patients achieve discharge criteria [Moore *et al.* 1998].

Adrenaline added to epidural bupivacaine accelerated the onset of analgesia [Eisenach *et al.* 1987] and amplified the degree of the motor block during labour [Eisenach *et al.* 1987; Laishley and Morgan 1988]. It increases the duration of epidural anaesthesia with shorter-acting local anaesthetics but not with longer-acting agents such as bupivacaine [Kopacz *et al.* 2001]. When added to epidural lidocaine or bupivacaine, adrenaline decreased the peak plasma concentrations of the local anaesthetics [Burm *et al.* 1986; Kopacz *et al.* 2001]. It is assumed that adrenaline can delay the absorption and enhance the anaesthetic and analgesic action of local anaesthetics and opioids in the epidural space [Covino and Wildsmith 1998; Niemi and Breivik 1998].

In a series of clinical studies, adrenaline in dosages of about 10–20 µg/h produced several beneficial effects when added to TEA, including improved pain relief [Niemi and Breivik 1998; Sakaguchi *et al.* 2000; Niemi and Breivik 2002], reduced opioid requirement [Baron *et al.* 1996], and lowered opioid plasma concentrations [Baron *et al.* 1996; Niemi and Breivik 1998]. These were accompanied with either a reduced [Niemi and Breivik 1998; Niemi and Breivik 2002] or an unaffected [Baron *et al.* 1996; Sakaguchi *et al.* 2000] incidence of side-effects. In a dose-response finding study of TEA after major thoracic or upper abdominal surgery, the minimally effective concentration of adrenaline required to maintain relief of dynamic pain was 1.5 µg/ml (18 µg/h on average) when added to bupivacaine 1 mg/ml and fentanyl 2 µg/ml [Niemi and Breivik 2003].

Adrenaline seems to be a useful adjuvant for thoracic CEA, but its value in lumbar CEA remains contradictory [Curatolo 2002]. The addition of adrenaline 0.5 µg/ml [Cohen *et al.* 1998] and 1.0 µg/ml [Cohen *et al.* 1992] to an epidural combination of bupivacaine and fentanyl after caesarean section gave no benefit except for a slightly lower infusion rate in the group with the adrenaline concentration of 1.0 µg/ml [Cohen *et al.* 1992]. In these two studies, adrenaline doses were about 8 µg/h (with additionally patient controlled boluses, maximum 9 µg/h) [Cohen *et al.* 1998], and 14 µg/h (with on demand epidural boluses, maximum 5 µg/h) [Cohen *et al.* 1992]. The discrepancy between TEA and LEA could be due to anatomical differences, such as the distance between the site of administration and the site of the α_2-adrenergic receptors in the spinal dorsal horn level [Curatolo *et al.* 1997]. By increasing the dosage of adrenaline added to LEA it might be possible to increase the availability of adrenaline at the spinal cord level and thereby to improve the epidural analgesia transmitted through α_2-adrenergic receptors.

Clonidine

Following local anaesthetics and opioids, clonidine is the most studied drug used for human neuraxial analgesia [Maze and Tranquilli 1991]. It has been implemented as an adjuvant drug in miscellaneous regional anaesthesia techniques [Eisenach *et al.* 1996], including CEA [Armand *et al.* 1998]. Clonidine is moderately lipid soluble and easily penetrates the blood-brain barrier leading to spinal and supraspinal receptor binding. Although the systemic administration of clonidine can provide analgesia, its primary site of antinociceptive action appears to be at the spinal level [Bernard *et al.* 1995; Eisenach *et al.* 1996; Eisenach *et al.* 1998]. Similar to epidural adrenaline (see above), epidural clonidine produces segmental hypoalgesia to painful stimuli [Curatolo *et al.* 1997].

In a dose-response study, epidural clonidine 3–10 μg/kg (maximum 900 μg) yielded analgesia in a dose-dependent manner after abdominal surgery or TKA and with 700–900 μg it produced complete analgesia lasting 4–6 h. Such high doses, however, caused the typical, dose-dependent side-effects related to clonidine, *i.e.*, hypotension, bradycardia, and sedation [Eisenach *et al.* 1989]. With regard to CEA, clonidine alone achieved adequate pain relief at infusion rates of 100–150 μg/h [De Kock *et al.* 1997], but, again, with the typical side-effects related to high doses of clonidine.

Given by the spinal or epidural route, clonidine as an adjunct to local anaesthetics usually prolongs the effect of the latter [Racle *et al.* 1987; Eisenach *et al.* 1996]. Interestingly, clonidine by mouth prolonged lidocaine spinal anaesthesia [Liu *et al.* 1995]. Intravenous clonidine delivered effective postoperative analgesia, for example, following correction of scoliosis [Bernard *et al.* 1995]. Clonidine 50 μg/h along with levobupivacaine (7.5 mg/h) gave superior CEA than did either drug individually after hip replacement [Milligan *et al.* 2000]. On the other hand, uncertainty exists as to whether clonidine can prolong the effect of epidural or spinal administered opioids [Walker *et al.* 2002]. Nevertheless, some investigations showed a synergistic pain relief, e.g. when combining clonidine with morphine [Spaulding *et al.* 1979; Petit *et al.* 1989] or sufentanil [Vercauteren *et al.* 1990]. Regarding the latter example, epidural bolus administration of sufentanil 25 μg with clonidine 1 μg/kg offered superior analgesia after caesarean section as compared to sufentanil 50 μg alone. This benefit, however, was achieved at the cost of hypotension [Vercauteren *et al.* 1990]. With respect to continuous neuraxial analgesia, the combination of clonidine and morphine as an epidural infusion enhanced analgesia following major abdominal surgery [Motsch *et al.* 1990]. Similar to this, the addition of clonidine in dosages of maximum 37.5 μg/h [Vercauteren *et al.* 1994] and 0.03 μg/kg/h [Delaunay *et al.* 1993] reduced the requirements of epidural sufentanil after caesarean section and fentanyl following abdominal surgery, respectively.

Only a limited number of studies have attempted to exploit the possible benefits of clonidine when added to a CEA of an opioid together with a local anaesthetic [Mogensen *et al.* 1992; Paech *et al.* 1997]. TEA was improved by giving clonidine 18.75 μg/h together with bupivacaine (5 mg/h) and morphine (0.1 mg/h) after hysterectomy [Mogensen *et al.* 1992], or by administering clonidine 20 μg/h along with bupivacaine (6.25 mg/h) and fentanyl (10 μg/h) after abdominal gynaecological surgery [Paech *et al.* 1997]. However, these clonidine regimens were associated with hypotension and bradycardia. Although generally well tolerated by the patients, these untoward effects have been considered problematic in the postoperative setting.

In an effort to determine the most beneficial combinations of bupivacaine, fentanyl, and clonidine for TEA [Curatolo *et al.* 2000] and LEA [Sveticic *et al.* 2004], several drug mixtures were identified as being ‘optimal’ (Table 3 and Table 4), referring to such combinations which provide adequate pain relief with minimal side-effects. The authors, however, highlighted that their results (Table 3 and Table 4) were not conclusive ones but instead point towards combinations worthy of being investigated further in future CEA studies.

It remains unknown as to whether epidural clonidine in reduced amounts, *e.g.*, <15 µg/h, may still contribute to the efficacy of a CEA consisting of a mixture of low-dose local anaesthetic and opioid without causing any significant degree of hypotension, bradycardia, and sedation.

Table 3. *Results from a search for optimal combinations of bupivacaine, fentanyl, and clonidine for TEA after major abdominal surgery (data from [Curatolo et al. 2000]).*

	Combination 1	*Combination 2*	*Combination 3*
Bupivacaine (mg/h)	9	8	13
Fentanyl (µg/h)	21	30	25
Clonidine (µg/h)	5	0	0
Infusion rate (ml/h)	7	9	9

Data are doses of component drugs or infusion rates as indicated. From a longer list of investigated drug mixtures, Combinations 1–3 were identified by the authors [Curatolo *et al.* 2000] as 'optimal', referring to combinations providing adequate pain relief with minimal side-effects. TEA=Continuous epidural analgesia at thoracic level.

Table 4. *Results from a search for optimal combinations of bupivacaine, fentanyl, and clonidine for LEA after knee or hip surgery (data from [Sveticic et al. 2004]).*

	Combination 1	*Combination 2*	*Combination 3*	*Combination 4*
Bupivacaine (mg/ml)	1.0	0.9	0.6	0.5
Fentanyl (µg/ml)	1.4	3.0	2.5	2.4
Clonidine (µg/ml)]	0.5	0.3	0.8	1.0

Data are concentrations of component drugs. From a longer list of investigated drug mixtures, Combinations 1–4 were identified by the authors [Sveticic *et al.* 2004] as 'optimal', referring to combinations providing adequate pain relief with minimal side-effects. LEA=Continuous epidural analgesia at lumbar level. Initial infusion rate 7 ml/h, increased by 2 ml/h to a maximum of 15 ml/h; additionally, nurse administered 5-ml boluses (lockout time 60 min) for breakthrough pain.

Other adjuvants

The list of possible adjuvants to neuraxial analgesia is expanding as the understanding of the complex pain transmission and modulation at the spinal cord level and in the brain become more clear [Gordh 1992; Walker *et al.* 2002; Buckenmaier and Bleckner 2005]: Apart from α_2-adrenergic agonists, many other substances have been tested in clinical regional anaesthesia, *e.g.*, ketamine, magnesium, neostigmine, midazolam, and droperidol. Ketamine, an N-methyl-D-aspartate receptor antagonist, may improve pain relief and reduce overall opioid requirements when added to an epidural opioid with or without a local anaesthetic [Subramaniam *et al.* 2004]. On the other hand, a study in rats suggested that the additive or synergistic antinociceptive effect of the adjuvant ketamine might not be generalizable to all opioids [Hoffmann *et al.* 2003]. Magnesium can express antinociceptive action through the blockade of N-methyl-D-aspartate receptors [Kroin *et al.* 2000; Buvanendran *et al.* 2002]. Neostigmine, by augmenting the muscarinic cholinergic activity at spinal level, may reduce postoperative analgesic requirements [Liu *et al.* 1999; Almeida *et al.* 2003]. Whatever the potential benefits of such neuraxial adjuvant drugs, one must keep in mind possible side-effects, for example, nausea with neostigmine [Almeida *et al.* 2003] and psychomimetic actions with ketamine [Kathirvel *et al.* 2000], as well as safety concerns [Hodgson *et al.* 1999; Eisenach and Yaksh 2003; Yaksh and Allen 2004].

In addition to adrenaline, other drugs with vasoconstrictive actions have been studied as adjuncts to neuraxial anaesthesia, *e.g.*, the selective α_1-agonist phenylephrine which acts on spinal cord and dural blood flow without causing spinal ischaemia [Kozody *et al.* 1984]. The use of phenylephrine, however, has not gained popularity because it increased the frequency of transient radicular symptoms when added to spinal tetracaine [Sakura *et al.* 1997].

Safety considerations and compatibility of drug mixtures

Before applying an adjuvant, possible risks related to its use should be considered, *e.g.*, neurotoxicity. Furthermore, chemical and physical compatibility of the various compounds must be assessed, as should the stability of the infusions over periods of time.

Adrenaline and clonidine

Adrenaline possesses a strong vasoconstrictive potential and therefore one may question whether its administration through the neuraxis could induce ischaemic spinal cord injury. Indeed, in rats, adrenaline worsened spinal cord injury when added to intrathecal lidocaine 50 mg/ml [Hashimoto *et al.* 2001], as it did when given with tetracaine 10–20 mg/ml in rabbits [Oka *et al.* 2001]. However, it is uncertain as to whether these findings can be extrapolated to humans. Possibly the observed adverse effect may be due secondarily to a decreased systemic uptake of, and protracted exposure to lidocaine and tetracaine, rather than ischaemic side-effects because adrenaline alone in similar doses did not provoke neurotoxicity [Hashimoto *et al.* 2001; Oka *et al.* 2001]. In a review, it was reasoned that the data from animal studies and from experience gathered in humans over a century suggest that adrenaline is indeed a safe adjunct in routine neuraxial anaesthesia [Neal 2003].

Neuraxial clonidine is considered to be free from neurotoxic effects [Hodgson *et al.* 1999], even after prolonged intrathecal infusion [Gordh *et al.* 1986].

Compatibility and stability of drug mixtures

Various mixtures of local anaesthetics, opioids, and adjuvant drugs have been found compatible and stable for weeks [Christie *et al.* 1992; Wulf *et al.* 1994; Oster Svedberg *et al.* 2002]. Adrenaline is prone to oxidation when exposed to light and therefore sodium metabisulphite and disodium edetate are often added as preservatives to adrenaline preparations. With these preservatives, adrenaline remained stable for up to 20 days at 3 or 23 °C when added to bupivacaine hydrochloride and fentanyl citrate [Dawson *et al.* 1992].

Side-effects and complications related to neuraxial anaesthesia and analgesia

General aspects

Side-effects can be regarded as indicators for the safety (hypotension, respiratory depression) and the tolerability (motor weakness, nausea, itching, etc.) of the neuraxial techniques. Side-effects may limit the provision of effective postoperative analgesia and have been recently quantified in anaesthetic practice with special attention given to respiratory depression, hypotension, sedation, postoperative nausea and vomiting (PONV), pruritus, motor block, and urinary retention after parenteral opioid and epidural analgesia (Table 5 and Table 6) [Block *et al.* 2003; Cashman and Dolin 2004; Dolin and Cashman 2005].

In a multicenter prospective survey including more than 40 000 spinal and 35 000 epidural anaesthetics, serious events such as cardiac arrest, severe neurological injury, respiratory failure,

and seizures were reported in 1:1 250 and 1:5 000 patients, respectively [Auroy *et al.* 2002]. Neurological sequelae after neuraxial anaesthesia is not always related to the anaesthetic technique itself but may arise *de novo*; additionally, conditions such as diabetes mellitus and previously unrecognized neurological disorders may be associated with new perioperative neurological findings [Hebl *et al.* 2006a; Hebl *et al.* 2006b].

Possible side-effects and complications related to postoperative neuraxial analgesia must be taken into account when planning the treatment strategies and counterbalanced with possible problems seen with other forms of acute postoperative pain therapy. The patients should have adequately educated, dedicated, and vigilant personnel [Rawal and Berggren 1994; Salomäki *et al.* 1996]. Awareness, immediate diagnosis, and appropriate treatment of whatever inadvertent event that may occur are the foundation for the safe provision of neuraxial techniques.

Table 5. Incidence rates for hypotension, PONV, pruritus, and motor blockade when comparing CEA (local anaesthetic with or without opioid) with parenteral opioids (PCA and intramuscular opioids) for postoperative analgesia based upon a recent meta-analysis of 100 RCTs performed in adults [Block et al. 2003].

	CEA	*Parenteral opioids*	*Comment*
Hypotension	8–14	2–14	Hypotension more frequent with TEA compared to LEA
PONV	26–42	25–72	Significant difference for LEA (42%) *versus* parenteral opioids (72%); however, if CEA with opioid alone, incidence rate even 45%–80%
Pruritus	2	0	If LEA with opioid alone, incidence rate even 38%
Numbness and motor blockade	1–2	0–1	

Data are incidence rates (%). PONV=Postoperative nausea and vomiting. CEA=Continuous epidural analgesia. PCA=Patient controlled analgesia with intravenous opioid. RCT=Randomized controlled trial. TEA and LEA=CEA given at thoracic or lumbar level, respectively.

Respiratory depression

The risk of respiratory depression from epidural analgesia utilizing an opioid is dose-dependent and occurs at a frequency of 0.1–1.2% [Stenseth *et al.* 1985; Ready *et al.* 1991; Scott *et al.* 1996; Cashman and Dolin 2004]. This incidence does not differ from that seen with systemic opioids [Mulroy 1996; Cashman and Dolin 2004]. The incidence of respiratory depression seems to have decreased during the period 1980-1999 [Cashman and Dolin 2004]. CEA utilizing fentanyl in dosages of 10–20 µg/h apparently rarely causes respiratory depression [Breivik 1992], while at dosages of 100–125 µg/h severe respiratory insufficiency can occur [Weightman 1991].

Several conditions may place patients at a greater risk of respiratory depression such as increased age, sleep apnoea, and chronic lung conditions. Respiratory depression from lipophilic opioids such as fentanyl may occur within 2 h of a bolus dose whereas in the case of a hydrophilic opioid as morphine, 6–12 h (or even more) may elapse before this might be manifested. This is because of the slow rostral migration within the cerebrospinal fluid (CSF) to the brain stem. Thus, a risk of delayed respiratory depression might be expected at least with higher bolus doses of morphine [Bailey *et al.* 1993].

The respiratory rate alone is not always a reliable predictor of looming respiratory depression but the degree of sedation should be monitored as well [Bailey *et al.* 1993; Mulroy 1996]. If the respiratory rate is <10/min or somnolence occurs the following measures should be taken: an

attempt to arouse the patient, reduction or interruption of the infusion, as well as the consultation of an anaesthetist. Severe respiratory insufficiency should immediately prompt: offering supplemental oxygen, ventilation with mask (or even endotracheal intubation), and administration of an opioid antagonist, *e.g.*, naloxone 0.1 mg i.v. (to be repeated, if required) [Salomäki *et al.* 1996].

Table 6. Incidences of adverse effects registered during acute postoperative pain management with CEA, PCA, and intramuscular opioids based upon a recent review of the literature including 165 publications [Cashman and Dolin 2004; Dolin and Cashman 2005].

	CEA	*PCA*	*Opioid i.m.*	*All together*
Respiratory depression[a]				
Respiratory rate	1.1 (0.6–1.9)	1.2 (0.7–1.9)	0.8 (0.2–2.5)	1.1 (0.7–1.7)
SpO_2	15 (5.6–35)	12 (5.6–22)	37* (23–46)	17 (10–27)
Naloxone	0.1* (0.1–0.2)	1.9 (1.9–2.0)	1.4 (0.1–13)	0.3 (0.1–1.3)
Hypotension[b]	5.5* (3.2–9.3)	0.7* (0.2–2.4)	3.6 (2.0–6.4)	4.7 (2.8–7.7)
Nausea				
Females only	39 (26–54)	53 (37–63)	58 (27–73)	53 (45–61)
Females and males	19 (14–25)	32* (27–38)	17 (6.6–37)	25 (19–32)
Vomiting				
Females only	30 (24–37)	21 (14–31)	49 (36–63)	34 (25–44)
Females and males	16 (13–21)	21 (17–25)	22 (17–28)	20 (18–23)
Sedation				
Mild	14* (14–15)	57 (54–59)	54 (48–59)	24 (23–25)
Excessive	1.2* (0.9–1.4)	5.3 (4.6–6.4)	5.2 (4.1–6.4)	2.6 (2.3–2.8)
Pruritus	16 (13–20)	14 (11–18)	3.4* (1.6–6.9)	15 (12–18)
Urinary retention	29* (22–38)	13 (6.6–25)	15 (9.3–23.8)	23 (17–30)

Data are mean (95% CI) incidence rates (%); numbers >10% were rounded. CEA=Continuous epidural analgesia. PCA=Patient controlled analgesia (intravenous). SpO_2=Oxygen saturation measured by pulse oximetry.

*Influence of analgesic technique statistically significant.
[a]Respiratory depression as indicated by respiratory rate, SpO_2 lower than predetermined value, or by the need for the opioid-antagonist naloxone.
[b]Hypotension as indicated by arterial pressure below predetermined level, or by any other definition.

Motor blockade

When pronounced, numbness and motor blockade of the lower extremities from continuous neuraxial analgesia may delay the ever important start of physiotherapy. Motor blockade is the side-effect most often attributable to CEA when compared to opioids given parenterally; an incidence of 1%–3% has been reported depending on whether CEA was given at a lumbar or thoracic level and whether the infusion included an opioid in addition to the local anaesthetic or not [Liu *et al.* 1998; Wheatley *et al.* 2001; Block *et al.* 2003].

Recurrence of motor blockade during CSPA became a problem with 1–2 mg/h bupivacaine infused after orthopaedic surgery [Niemi *et al.* 1996; Bachmann *et al.* 1997]. Replacing bupivacaine by ropivacaine in CSPA may prove to be advantageous with regard to the incidence and degree of motor blockade because of ropivacaine's potential for a better sensory-motor differential block (similar sensory, but less pronounced motor block with ropivacaine as compared to bupivacaine) [Rosenberg and Heinonen 1983; Brockway *et al.* 1991; Zaric *et al.* 1996; McClure 1996; Brodner *et al.* 1999].

In case of disturbing motor blockade during CEA or CSPA, the local anaesthetic dose administered should be reduced or even temporarily stopped. Physicians and nurses should always be aware that a reoccurring or deepening motor block of the lower extremities during continuous neuraxial analgesia may be an early indicator of epidural haematoma [Horlocker and Wedel 1998].

Postdural puncture headache (PDPH)

PDPH may occur after a deliberate or accidental (which may even be unrecognized) breach of the dura mater and it generally presents itself within the first two days after puncture [Turnbull and Shepherd 2003]. Most patients with PDPH complain of a fronto-occipital headache that manifests itself on standing but eases on lying supine. The incidence of PDPH might well be related to the needle size and type (higher incidences with cutting wide bore needles as compared to thin needles with a pencil-point design) [Turnbull and Shepherd 2003]. The rate of PDPH has been connected to the degree of loss of CSF which again is related the size of the needle [Holst *et al.* 1998]. In case of PDPH, the patient should be reassured about the benign nature of the headache which resolves spontaneously in the majority of cases. Conservative measures to treat PDPH include bed rest, hydration, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and caffeine [Turnbull and Shepherd 2003]. An epidural blood patch is indicated if conservative management remains ineffective and PDPH is severe or may extend the duration of hospital stay [Turnbull and Shepherd 2003].

Since the first catheter technique for CSA was described [Tuohy 1944], there were concerns that CSA would present high incidences of PDPH. Such contention has been fuelled, for example, by a report showing an overall PDPH incidence of 78% in a population of 18 volunteers (18–30 years; enrolled in a neuroendocrinological study in which CSF samples were drawn through a spinal catheter) [Gosch *et al.* 2005]. This high PDPH incidence, however, is in contrast to other studies [Denny *et al.* 1987; Mahisekar *et al.* 1991]. For instance, a single case of PDPH was noted in 117 surgical patients in whom a 20G catheter was placed through an 18G needle [Denny *et al.* 1987]. In a survey with more than 3 200 patients, the frequency of PDPH was similar for SSA, CSA, and combined spinal-epidural anaesthesia (0.9%, 1.5%, and 1.7%, respectively) [Puolakka *et al.* 2000a]. The initial reports regarding 32G catheters showed an incidence of 4% [Hurley and Lambert 1990] with complete absence of PDPH in elderly patients [Silvanto *et al.* 1992; Pitkänen *et al.* 1992b].

In addition to the thickness of the needle and catheter, one further explanation for the variation in the incidences of PDPH reported may be the timing of catheter removal. In the above mentioned report with a PDPH incidence of 78%, the catheters were removed 4 h after puncture [Gosch *et al.* 2005]. It has been postulated that an inflammatory reaction in the dura mater and the arachnoid surrounding the puncture hole produces oedema to such a degree that the site becomes sealed soon after removal of the catheter [Denny *et al.* 1987]. However, with early catheter removal (after surgery) the inflammatory reaction might not have sufficiently developed and thus the sealing process is impeded permitting a prolonged loss of the CSF into the epidural space.

Neurological complications

Persistent neurological injury associated with neuraxial anaesthesia is fortunately rare. In an analysis based on patient insurance claims in Finland, it was estimated that serious complications occur in about 1:22 000 of spinal and 1:19 000 of epidural anaesthesias [Aromaa *et al.* 1997]. In all, the risk of neurological damage related to the placement of an epidural catheter or infusion is low [Auroy *et al.* 1997; Auroy *et al.* 2002]. A recent retrospective study of severe neurological complications after central neuraxial blockades for the period 1990–1999 produced the following results [Moen *et al.* 2004]. Approximately 1 260 000 spinal blocks and 450 000 epidural blocks were carried out, which included 200 000 epidural blocks for the relief of labour pain. The complications numbered 127 and included spinal haematoma (n=33), cauda equina syndrome (n=32), meningitis (n=29), epidural abscess (n=13), and miscellaneous problems (n=20). Permanent neurological damage was observed in 85 patients (1:20 000). The incidence of complications ranged from 1:20 000 to 1:30 000 for spinal blockade in all patient groups. As a result of obstetrical epidural blockade, the incidence was 1:25 000 while in the remaining epidural anaesthetics the incidence was 1:3 600 [Moen *et al.* 2004]. In that particular study, complications occurred significantly more often with epidural blockade than after spinal anaesthesia which is opposite to earlier observations [Aromaa *et al.* 1997; Auroy *et al.* 1997; Auroy *et al.* 2002]. Furthermore, the data suggests that obstetric patients carry a significantly lower incidence of complications while osteoporosis might be a previously neglected risk factor [Moen *et al.* 2004].

Radiculopathy following spinal or epidural anaesthesia is connected with paraesthesia or pain experienced at the time of needle insertion or drug injection [Auroy *et al.* 1997; Horlocker *et al.* 1997b]. If pain were to occur during the injection, one should immediately stop the injection and withdraw the needle.

Epidural haematoma

Instrumentation during neuraxial anaesthesia is connected to the risk of vascular trauma within the spinal canal and epidural haematoma formation. Although rare, it is a potentially hazardous complication with compression of neural tissues in the spinal canal and permanent neurological sequelae. The incidence of epidural haematoma is estimated at <1:220 000 after spinal and <1:150 000 after epidural anaesthesia techniques [Tryba 1993]. Spinal haematoma after obstetric epidural blockade carried the incidence of 1:200 000, dwarfing the incidence of 1:3 600 described in female subjects who had undergone TKA [Moen *et al.* 2004]. A review article covering epidural haematoma cases from 1906 to 1994 disclosed that spinal anaesthesia was associated with 15 and epidural anaesthesia with 46 haematomas [Vandermeulen *et al.* 1994]. In 68% of instances, haemostatic abnormalities were present, while 25% of them were associated with either difficult or bloody catheter insertion [Vandermeulen *et al.* 1994]. In 15 of 32 patients with an epidural catheter, the haematoma manifested itself soon after catheter removal [Vandermeulen *et al.* 1994]. Therefore, this complication must always be kept in mind during the maintenance and after removing the catheter.

The typical signs of an epidural haematoma are acute back pain, bowel incontinence, urinary bladder dysfunction, in addition to motor and sensory deficits of the legs. Often the patients who have already recovered from spinal or epidural anaesthesia begin to experience motor and sensory blockade. Back pain may be severe, radiate to the legs, and begin before the development of neurological signs and symptoms. A low level of suspicion, prompt confirmation of the diagnosis (preferentially with magnetic resonance imaging), and swift (<6–8 h) surgical evacuation (if necessary) are required to prevent permanent neurological sequelae.

Several reviews and national guidelines are available to help the clinician in estimating the patient's coagulation status and antithrombotic medication [Gogarten *et al.* 2003; Horlocker *et al.* 2003; Bombeli and Spahn 2004; Niemi and Lassila 2004]. For instance, intraoperative heparinization in vascular surgery during arterial clamping should be delayed for at least 1 h after neuraxial instrumentation.

The occurrence of symptomatic haematomas following intraoperative anticoagulation in vascular surgery patients with epidural or spinal catheters seems to be rare assuming proper patient selection, an atraumatic technique, and appropriate monitoring of anticoagulant activity [Rao and El-Etr 1981; Raggi *et al.* 1987; Ellis *et al.* 1995].

Infections

Epidural abscess is a rare complication which, however, can lead to permanent neurological injury. Abscesses have been reported both after epidural anaesthesia [Ngan Kee *et al.* 1992] and chronic epidural catheterization [Du Pen *et al.* 1990]. The signs and symptoms of an epidural abscess may be similar to those of epidural haematoma; however, the patient may in addition develop a fever. Diagnosis is best with magnetic resonance imaging and treatment choices span from intravenous antibiotics to percutaneous drainage and surgical intervention.

Meningitis associated with central neuraxial techniques is rare with the majority of cases due to bacterial nosocomial infection. Meningitis may present itself with headache, nausea, vomiting, photophobia, nuchal rigidity, and fever. Diagnosis is by CSF examination and culturing, and by treatment with antibiotics.

Up to 5% of skin puncture sites may become inflamed when an epidural catheter is left *in situ* for >24 h. While this may not indicate an infection in itself, cellulites or purulent discharge from the puncture site should prompt catheter removal, initiation of an empiric antibiotic, and culturing of the catheter tip.

There appear to be no reports of serious infections with CSA [Horlocker *et al.* 1997a]. Occasionally, microbiological testing was positive for Staphylococcus epidermidis when culturing spinal catheter tips 24 h after catheter placement [Lindgren *et al.* 1995; Standl *et al.* 1995b]. These findings probably represented only contamination from normal skin flora. There are no prospective trials looking into the incidence of infective complications with spinal catheters. In most studies postoperatively, spinal catheters were left *in situ* for a maximum of 1–2 days.

The use of continuous neuraxial anaesthesia and analgesia requires meticulous aseptic technique during insertion and maintenance of the catheter which as well includes the use of a bacterial filter.

Technical problems related to neuraxial techniques

Rates of technical failure have been reported to be comparable for SSA, CSA, and combined spinal-epidural anaesthesia (1.0%, 1.5%, 1.0%, respectively) [Puolakka *et al.* 2000a]. CEA can fail

because of technical problems in as much as 6%–25% of cases, with many centres reporting failure rates of 10%–20% [Block *et al.* 2003]. A recent audit at the Meilahti Hospital, Helsinki University Hospital – where Studies I and V were carried out – revealed CEA related technical problems to range from 10%–15% in gastroenterological, thoracic, vascular, and urologic surgery in the years 1997–2004 (E. Nilsson, personal communication, 2007).

The success rates for inserting intrathecal catheters were 90% with a 24G epidural catheter through a 19G Tuohy needle and a 28G microcatheter through a 22G spinal needle. On the other hand, success rate was 63% using the catheter-over-the-needle technique, *i.e.*, a 22G spinal catheter over a 27G spinal needle advanced through an epidurally placed 18G Crawford needle [Puolakka *et al.* 2000b]. The failure rate for inserting the very fine 32G catheters was encountered in some 25% of all instances [Silvanto *et al.* 1992; Pitkänen *et al.* 1992b; Guinard *et al.* 1993]. The various difficulties experienced with microcatheters were in passing the catheter through the needle, kinking, breakage, failure to aspirate, dislodgment of the adapter, and leakage through the adapter [Silvanto *et al.* 1992; Pitkänen *et al.* 1992b; Niemi *et al.* 1994; Puolakka *et al.* 2000b]. It should be mentioned that catheters with removable stylets have been developed to prevent kinking during the insertion.

Confirmation of epidural catheter position

In clinical routine, the identification of the epidural space by the LOR technique and the placement of an epidural catheter depend mainly on the experience acquired by the anaesthetist but without any visual control of the catheter position. The improper positioning of thoracic epidural catheters is believed to occur in 10%–15% of the patients [Rigg *et al.* 2002]. If the tip of the catheter is not properly situated in the epidural space, the analgesia will be most likely inadequate.

Failure to correctly identify the epidural space can be because of insufficient experience of the practitioner and more so due to anatomical anomalies. A ‘pseudo-LOR’ may transpire after a short distance of needle passage within the interspinous ligament because of cavity formation [Bromage 1954; Rissanen 1960; Davidson 1966; Sharrock 1979]. Such degenerative cavities are especially frequent in the elderly [Rissanen 1960] and may easily take up 10–20 ml of fluid or air used during the puncture [Sharrock 1979]. Similar degenerative changes in the ligamentum flavum have been described [Wildi *et al.* 2004; Asamoto *et al.* 2005]. A misleading LOR might also develop if the needle deviates from its intended course and enters the paravertebral muscles [Bonica 1956] or even the pleural cavity (*e.g.*, [Patermann *et al.* 2005]).

After identifying the epidural space and placing the catheter, the catheter may change its position with the patient’s movements [Hamilton *et al.* 1997]. The catheter can move 1–2 cm inward and outward during CEA, independent of whether the catheter has been tunnelled or sutured to the skin [Chadwick *et al.* 2003]. The catheter tip may even completely slip out of the epidural space. The incidence of premature catheter dislodgement is about 6%–12% [Scott *et al.* 1995; Dolin *et al.* 2002]. In addition, there are reports of delayed subarachnoid migrations, *i.e.*, dura perforations by the catheter [Robson and Brodsky 1977]. Subarachnoid migration bears the risk of total spinal anaesthesia [Skowronski and Rigg 1981].

Therefore, in the interest of the patient, routine confirmation of the catheter’s position must be carried out before CEA is initiated. The classical method to assure the correct position is to give a test dose of a local anaesthetic and after several minutes to check for signs of sensory blockade [Bromage 1954]. However, this test dose concept is not free of problems (see below) and thus various alternative methods have been suggested (*e.g.*, [Lewis *et al.* 1992; Tsui *et al.* 1998; Ghia *et al.* 2001; Lechner *et al.* 2003; Willschke *et al.* 2006]). One of these alternatives is the epidural

stimulation test (EST) [Tsui *et al.* 1998]. In the following, EST will be described in more detail and compared (Table 7) to epidurography as well as to the epidural test dose.

Table 7. Advantages and disadvantages of three techniques used to confirm the position of epidural catheters.

	Test dose	*EST*	*Epidurography*
Established in clinical routine	Yes	No	No, but proven beneficial in various circumstances
Indirect / direct method	Indirect, subjective	Indirect, objective muscle twitching	Direct visualization of catheter
Possible to perform bed-side	Yes	Yes	No (Yes only with mobile X-ray equipment)
Special epidural catheter	Not required	Required	Not required
Exposure to radiation	No	No	Yes
Adverse effects	Risk of total spinal anaesthesia	Not reported	Allergic reactions possible but serious adverse effects very rare
Results available	Sensory block may take 10–20 min to develop	Immediately during performance	Processing of X-ray film
Expenditures	Minor	Moderate	High

Test dose=Epidural test dose of local anaesthetic and assessment of sensory blockade. EST=Epidural stimulation test, *i.e.*, the assessment of motor response elicited by electrical neurostimulation. Epidurography=Epidural contrast medium and X-ray of the spine.

Epidural test dose

As mentioned above, the classical method of assuring the correct catheter position is to administer a test dose of a local anaesthetic [Bromage 1954], *e.g.*, 3 ml lidocaine 20 mg/ml with adrenaline 5 µg/ml [Poblete *et al.* 1999; Guay 2006b], and then to observe for signs of sensory blockade. However, sensory changes after such a test dose are often weak and barely assessable, particularly in the very young and elderly patient, as well as in the disorientated or heavily premedicated patient. Therefore, testing sensory blockade includes subjectivity of both the patient and the assessor (Table 7). As the sensory block may require 10–20 min to develop, it may create problems in the operation room because of time constraints. Still, it is an easy method requiring only basic equipment (Table 7). There is, however, the risk of test dose being inadvertently administered intrathecally which could result in sudden cardiovascular depression and total spinal anaesthesia. Therefore, corresponding patient monitoring and emergency equipment should always be on hand.

Epidural stimulation test (EST)

Tsui and colleagues proposed a potentially simple, fast, reliable, and safe method to assure the epidural catheter position [Tsui *et al.* 1998; Tsui *et al.* 1999b]: They applied electrical neurostimulation (1 Hz, 0.2 sec, maximum 16 mA) through the catheter and judged the position of the latter to be epidurally if muscle response in the torso or in the extremities would be elicited at a current of 1–10 mA. Instead, the catheter tip is considered to be outside the spinal canal when the motor response occurs at a current >10 mA or remains absent despite maximum stimulation, while twitching at <1 mA is a warning sign of an inadvertent subarachnoid catheter placement [Tsui *et al.* 1998].

This test has been named the epidural stimulation test (EST), and ‘Tsui test’ by the inventor. The advantages attributed to EST are that it is easily and quickly performed at the patient’s bedside with only moderate costs. In addition, because it produces a visible muscle twitching it should

prove more objective and reliable than an epidural test dose (Table 7). Thus, EST may prove beneficial especially in patients with limited verbal communication [Tsui *et al.* 1998]. Nevertheless, it remains an indirect method for the confirmation of epidural catheter placement (Table 7).

The EST technique was originally performed one or two days postoperatively in patients with a metal coil reinforced epidural catheter [Tsui *et al.* 1998]. The purpose of the metal coil within the lumen of the catheter is to aid in conducting the electrical impulse along the entire length of the catheter.

Technical preconditions for EST include that the epidural catheter is equipped with a metal wire [Tsui *et al.* 1998; Tamai *et al.* 2005; Tsui and Sze 2005] which goes along with somewhat increased costs compared to a standard epidural catheter (Table 7). Besides, the neurostimulator must have certain requirements regarding the amplitude and duration of impulse; otherwise, it may be difficult to compare results gained by different study groups [Charghi *et al.* 2007]. The use of EST is contraindicated in individuals with pacemakers and other implanted electrical devices [Tsui *et al.* 1998].

EST has been subject of several reports [Tsui *et al.* 1999c; Tsui *et al.* 1999a; Tsui *et al.* 2000; Goobie *et al.* 2003; Tsui *et al.* 2004a; De Medicis *et al.* 2005; Tsui *et al.* 2007; Charghi *et al.* 2007], but as yet has not been widely accepted in clinical routine. So far, it seems not to have been employed repeatedly during postoperative CEA. The repetition of EST might be of particular interest when an initially well working CEA begins to fail to produce adequate analgesia and where the catheter tip is suspected of no longer being within the epidural space.

Epidurography

Epidurography was introduced as an X-ray diagnostic method in 1926 [Sicard and Forestier 1926]. By administering 3–15 ml of contrast medium through the epidural catheter followed by a radiogram of the spinal column, it is possible to visualize the position of the catheter (*e.g.*, [Wulf *et al.* 1993; Du Pen *et al.* 1996; Collier 1998]). Thus, epidurography is a direct method to confirm the position of the catheter as compared to the indirect epidural test dose and EST (Table 7). Excluding patients with thyrotoxicosis or iodine-allergy and with the use of water-soluble iodinated contrast media, epidurography is a safe procedure [Collier 1998]. Adverse reactions to the epidural administration of contrast medium are generally rare and transient in nature. These include local pressure sensation, feeling of warmth, metallic taste on accidental intravascular application, and allergic reactions. Although the latter are mostly mild to moderate skin or respiratory reactions, severe allergic reactions such as hypotension, tachycardia or bradycardia, and seizures have been reported.

Attempts to correlate the spread of contrast solution in the epidurogram with the extent of nerve block met with only limited success. In other words, adequate epidural analgesia with bilateral blockade does not correlate with bilateral and symmetrical diffusion of contrast into the epidural space [Collier 1998; Hogan 1999; Motamed *et al.* 2006]. Nonetheless, epidurography in most instances reveals whether or not the catheter lies in the epidural space. It has become a valuable tool in pain management [Wulf *et al.* 1993] and it has even been considered for routine quality assurance regarding CEA [Seeling *et al.* 1995]. However, it has not gained further popularity probably because there is a need for radiology staff, bulky equipment, and exposure to radiation of the patient (Table 7).

Assessment of pain intensity

Pain intensity should be also assessed during significant movement or activity rather than only at rest. These include measurement during flexion and extension of an operated joint or deep breathing and/or coughing following thoracotomy or abdominal surgery.

Various validated scores are available for the assessment of pain intensity. It is commonly estimated by either a categorical (verbal or numerical) rating scale or a so-called visual analogous scale (VAS), *e.g.*, a 10 cm long scale (linear or triangle shaped) indicating the range from 'no pain' to 'worst pain imaginable' [Sriwatanakul *et al.* 1983a; Sriwatanakul *et al.* 1983b]. Often patients, especially the elderly with visual defects may present difficulties with the standard 10-cm scale. Enlarging the VAS scale to 50 cm has addressed this problem [Tigerstedt and Tammisto 1988].

The Prince Henry Hospital pain score (PHH-score) [Pybus and Torda 1982] and its modified form [Torda *et al.* 1995] have been devised specifically for the evaluation of pain after abdominal or thoracic surgery by examining the effect of analgesia on deep breathing and coughing. The modified PHH-score is defined as follows [Torda *et al.* 1995]: PHH-score 3=pain at rest, PHH-score 2=pain during deep breathing, PHH-score 1=pain on coughing, PHH-score 0=no pain on coughing.

Aims of the Study

The primary hypothesis of this study was to determine whether the efficacy and quality of continuous neuraxial postoperative analgesia might be improved by the use of adjuvant drugs and by technical means. The following issues were of specific interest:

1. To investigate whether adrenaline in concentrations of 2 μg/ml (Study I) and 4 μg/ml (Study II) added to low-dose ropivacaine-fentanyl mixtures improves the continuous epidural analgesia given at a lumbar level after arterial bypass surgery (Study I) and total knee arthroplasty (Study II), respectively.
2. To assess whether low-dose clonidine (6–14 μg/h) enhances lumbar continuous epidural analgesia when added to a low-dose infusion of ropivacaine and fentanyl following total knee arthroplasty (Study III).
3. To study the feasibility of a continuous spinal anaesthesia technique utilizing a microcatheter in patients undergoing arterial bypass surgery of the lower extremities (Study IV), and to examine the analgesic efficacy of a continuous spinal infusion of ropivacaine alone (maximum 2 mg/h) or one of ropivacaine together with morphine (maximum 1 mg/h and 8 μg/h, respectively) after arterial bypass surgery on the legs with special attention paid to motor blockade (Study IV).
4. To evaluate the feasibility of the epidural stimulation test to determine the position of the epidural catheter at the time of its placement and then its position during continuous epidural analgesia in patients undergoing major abdominal surgery or thoracotomy (Study V).
5. To register and analyze possible technical problems which may occur during continuous epidural and spinal anaesthesia and analgesia (Studies I–V).

Patients and Methods

Study designs and randomization

The study protocols were approved by the Ethics Committee of Helsinki University Hospital (I–V) and by the National Agency for Medicines (I–IV). Written informed consent was obtained from all study patients before the procedures.

Table 8 presents an overview of the types of surgery, anaesthesia, postoperative analgesia, drugs for postoperative analgesia, and other methodological aspects of Studies I–V.

Table 8. Outline of methods applied in Studies I–V.

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Surgery	Lower extremity arterial bypass	TKA	TKA	Lower extremity arterial bypass	Major abdominal or thoracotomy
Anaesthesia	SSA	SSA	SSA	CSA	GA
Neuraxial analgesia technique	CEA	CEA	CEA	CSPA	CEA
Drugs used for CEA and CSPA	Ropivacaine + Fentanyl ± Adrenaline	Ropivacaine + Fentanyl ± Adrenaline	Ropivacaine + Fentanyl ± Clonidine	Ropivacaine ± Morphine	Ropivacaine + Fentanyl
Other aspects	ABPI and plasma concentrations				EST and epiduro-graphy

TKA=Total knee arthroplasty. SSA=Single-dose spinal anaesthesia. CSA=Continuous spinal anaesthesia. GA=General anaesthesia. CEA=Continuous epidural analgesia. CSPA=Continuous spinal postoperative analgesia. ABPI=Ankle-brachial blood pressure index. EST=Epidural stimulation test. Symbol '±' stands for: Study group with, control group without this drug.

In the randomized, controlled trials (RCT), patients were randomized to either a study or a control group regarding the drugs given for CEA (I–III) and CSPA (IV) with the patients in the control groups receiving an active comparator medication. In Study IV, before randomization to either of the CSPA groups, each patient underwent intraoperative observation regarding the CSA technique. In the diagnostic, prospective Study V, no randomization was performed and all patients were treated according to the same trial protocol which included a standardized CEA.

Patients as well as physicians and nurses who were involved in the investigation were blinded as to the allocation of the study groups throughout the course of trials (I–IV). Block randomization together with the closed envelope method were used. The randomization envelopes were prepared by colleagues who did not take part in the study. The randomization codes were opened by an anaesthesia nurse at the time of the patient's arrival in the postanaesthesia care unit (PACU) after the operation. The nurse preparing the study drugs did not take any further part in the treatment or follow-up of that particular patient. After preparing the study drugs, the nurse placed the randomization code back into the envelope which again was sealed and kept among the patient's charts.

Patients, surgical procedures, and exclusion criteria

Patients enrolled to Study I and IV underwent arterial bypass surgery of the lower extremities. Patients in Studies II and III were scheduled for primary, unilateral TKA. Study V consisted of patients having major abdominal surgery (gastrointestinal or urologic) or thoracotomy.

Exclusion criteria included contraindications to the insertion of an epidural or spinal catheter such as haemostatic abnormalities and/or therapeutic anticoagulation, and infection at the puncture site. Patients on an adenosine diphosphate receptor antagonist or an inhibitor of the platelet receptor GPIIb/IIIa were excluded unless that drug had been discontinued well in advance as recommended [Niemi and Lassila 2004]. The other exclusion criteria are listed in Table 9.

Table 9. Exclusion criteria in addition to contraindications to insertion of an epidural or spinal catheter (see text) for Studies I–V.

Excluded if	*Study I*	*Study II*	*Study III*	*Study IV*	*Study V*
Age (years)	<18	<18 and >85	<18 and >85	<18	<18
ASA class	>IV	≥IV	≥IV	>IV	>IV
Renal insufficiency	Yes, if combined with renal replacement therapy	Yes	Yes	Yes, if combined with renal replacement therapy	Yes
Known allergy to NSAIDs	NA	Yes	Yes	NA	No
Heart insufficiency (NYHA classes III and IV)	No	Yes	Yes	No	No
BMI>36 kg/m^2	No	Yes	Yes	No	Yes
Iodide allergy	NA	NA	NA	NA	Yes
Pacemaker or other implanted electrical device	NA	NA	NA	NA	Yes

ASA class=American Society of Anesthesiologists physical status classification. NSAID=Non-steroidal anti-inflammatory drug. NA=Not applicable. NYHA=New York Heart Association classification. BMI=Body mass index.

Preoperative considerations and premedication

Before their operations, the patients received their normal morning medication, with angiotensin-converting enzyme inhibitors, diuretics, and drugs for diabetes mellitus being withheld. Thromboprophylaxis [Gogarten *et al.* 2003; Niemi and Lassila 2004] was initiated with dalteparin 5 000 IU s.c. (I, IV, and V) or enoxaparin 40 mg s.c. (II) in the evening before surgery followed by a corresponding amount of low-molecular weight heparin (LMWH) s.c. once daily (II and V) or dalteparin 2 500–5 000 IU s.c. twice daily as prescribed by the vascular surgeon (I and IV). In Study II, instead of LMWH some patients were given fondaparinux 2.5 mg s.c. once daily if the risk of deep vein thrombosis was considered high according to the recommendation of the internist. The initial dose of fondaparinux was given 6–9 h postoperatively. A variation of the thromboprophylaxis regimen was used in Study III consisting of dalteparin 2 500 IU s.c. one hour after the administration of the spinal anaesthesia, followed by 2 500 IU s.c. in the evening of that day – this was then followed with 5 000 IU s.c. once daily (based on [Hull *et al.* 2001]). The timing of placement and removal of epidural and spinal catheters in relation to LMWH and fondaparinux was according to recent guidelines [Gogarten *et al.* 2003; Niemi and Lassila 2004]. Catheter

placement and removal was not undertaken until at least 10 h had elapsed from the last dose of LMWH or 20 hours in patients with fondaparinux. Correspondingly, the consecutive LMWH or fondaparinux dose was withheld at least for 2 h after removing the catheter.

Premedication was with diazepam p.o. given 1 h before arriving in the operating theatre (I–V). The patients also received i.v. midazolam and fentanyl when needed for the insertion of the catheter (I–V), or for sedation and/or pain, *e.g.*, position-related discomfort, during the operation (I–IV).

Intraoperative monitoring included pulse oximetry, electrocardiogram (ECG), and non-invasive arterial blood pressure (II, III, and V). Invasive arterial pressure measurement was used in all patients from Studies I and IV and, when clinically indicated, in some patients of Study V. A central vein catheter for the measurement of central vein pressure (CVP) was inserted in all patients of Study IV, as it was in several patients of Studies I and V. All patients had a urinary catheter with hourly urine output being recorded (I–V).

Anaesthesia and other intraoperative aspects

Anaesthesia techniques

Table 10 summarizes details related to the anaesthesia techniques used in Studies I–V. Epidural catheters were placed prior to the puncture for spinal anaesthesia (I–III) or GA (V). The LOR technique was used to identify the epidural space. Spinal anaesthesia was provided with plain bupivacaine 5 mg/ml in Study I and with plain ropivacaine 7.5 mg/ml in Studies II–IV. The spinal anaesthesia was carried out with the patient in the lateral decubitus position in Studies I–III after which the patient was turned supine. On the other hand, in Study IV, the first dose of local anaesthetic was given through the intrathecal catheter only after the patient had been turned to the supine position. Epidural top-ups were permitted in Studies I–III in case of an early spinal block regression. In Study IV, intrathecally administered top-ups were an integral part of the CSA technique (Table 10). During the induction phase of Study IV, titration of the spinal anaesthesia with frequent top-ups was allowed with at least 3 min elapsing between two successive doses. The aim was to obtain a sensory block up to dermatome T10. The dermatomal spread of spinal anaesthesia was determined by testing for loss of cold sensation with an alcohol-soaked cotton swab 20 min after spinal anaesthesia was made (II and III). The sensory block (hypoaesthesia to cold) and motor blockade (modified Bromage scale, Table 13) were tested at 5 min intervals during the induction phase of Study IV until the degree of sensory block attained, at least, the level of dermatome T10.

Infusion therapy and haemostasis

The patients received Ringer's acetate solution 5–10 ml/kg i.v. before spinal anaesthesia (I–IV). In Study IV, this pre-loading was guided by the measurement of CVP (aiming at a CVP of ≥3 mmHg) before the first intrathecal dose of ropivacaine was injected. The intraoperative infusion therapy regimen consisted of Ringer's acetate, plasma expander, and transfusion of blood components as clinically indicated. The infusion therapy was adjusted according to urine output and blood loss.

In Studies I and IV, heparin 100 IU/kg i.v. was given 2 min before the artery was clamped. The need for additional heparin was evaluated by monitoring of the activated clotting time. Intravenous protamine and intra-arterial papaverine were injected at the discretion of the vascular surgeon.

A thigh tourniquet was applied during TKA (II and III). In Study III, tranexamic acid (Caprilon®, Leiras, Finland) 0.5–1.0 g i.v. was used to reduce bleeding when ordered by the

surgeon. In Study II, tranexamic acid 0.5 g i.v. was administered before inflation and again a short while before the release of the tourniquet.

Table 10. Anaesthesia.

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Position during puncture	Lat. decub.	Lat. decub.	Lat. decub.	Lat. decub.	Lat. decub. or sitting
Level epidural / spinal catheter	L1–2	L2–3 or L3–4	L2–3 or L3–4	L3–4 or L2–3	Thoracic level[a]
Catheter type	Perifix® or FlexTip Plus®	Portex®	Portex®	CoSpan®[b]	FlexTip Plus®
Epidural test dose	4 ml L 1% c. adr. 10 µg/ml	Study mixture, after surgery	3 ml R 0.75%	NA	3 ml + 3 ml L 2% c. adr. 5 µg/ml
Level spinal needle puncture	L3–4	L3–4 or L4–5	L3–4 or L4–5	See above	NA
Anaesthesia	SSA	SSA	SSA	CSA	GA
Drugs used for spinal anaesthesia	3 ml B 0.5%	3 ml R 0.75%	3–4 ml R 0.75%	Initially 1.0 ml R 0.75%	NA
Top-ups	Epidural, L 2% c. adr. 5 µg/ml	Epidural, R 0.75%	Epidural, R 0.75%	Spinal, 0.5 ml R 0.75%	R 0.75% at end of surgery

Lat. decub.=Lateral decubitus position, side to be operated on top. c. adr.=With adrenaline. L=Lidocaine. R=Ropivacaine. B=Bupivacaine. NA=Not applicable. SSA=Single-dose spinal anaesthesia. CSA=Continuous spinal anaesthesia. GA=General anaesthesia.
Perifix®=Epidural catheterization set, needle 18G, B. Braun, Germany.
FlexTip Plus®=Epidural Catheterization Set, needle 17G, catheter 19G, Arrow International Inc., Reading, USA.
Portex®=Epidural Minipack, needle 18G, Portex Ltd., Hythe, Kent, UK.
CoSpan®=Set for continuous spinal anaesthesia, Quincke needle 22G, catheter 28G, Kendall, Neustadt, Germany.

[a]At an appropriate thoracic intervertebral interspace with regard to the planned surgical incision.
[b]With Tuohy-Borst® adapter.

Intraoperative phase of Study IV

After the initial spinal dose of local anaesthetic, arterial pressure, CVP, and heart rate were recorded at 3 min intervals for 15 min and then every 5 min for the next 45 min. The sensory block and the motor blockade were evaluated every 5 min during the induction phase until the level of sensory block was above T10.

At the end of surgery, the surgeon was questioned at to whether the motor block had been satisfactory; and this was graded as: complete motor block – minor movements, manageable – movements to a disturbing degree.

General anaesthesia in Study V

Anaesthesia was induced intravenously with fentanyl and propofol followed by rocuronium to achieve muscle relaxation. Anaesthesia was maintained with sevoflurane in an air-oxygen mixture. Increments of intravenous fentanyl and rocuronium where given as needed. Sevoflurane was replaced by desflurane in four patients and by a combination of propofol and remifentanil infusions in three patients at the discretion of the attending anaesthetist.

Postoperative pain management

Continuous epidural and spinal analgesia

Table 11 shows some aspects of postoperative pain management including drug combinations and infusion rates used for CEA and CSPA. The infusion rates were regulated as needed in a stepwise manner, *i.e.*, decreased for hypotension or pronounced motor block and increased for surgical pain. In Study IV, in order to prevent accidental overdose, the display of the syringe pump used for CSPA was marked with alerting red tapes and a warning text that the infusion speed must not exceed 0.4 ml/h.

In Studies I–III, the postoperative epidural infusion was started when the dermatomal hypoaesthesia to cold had dropped to the level of the groin and first the voluntary contractions of thigh muscles were noted. In Study IV, the spinal infusion was begun with the first voluntary contractions of the thigh muscles. In Study V, the epidural infusion was started after the performance of the epidural nerve stimulations EST_4 (see below under heading 'Methods used in Study V' as well as Figure 1).

Table 11. Continuous epidural or spinal postoperative analgesia.

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
CEA or CSPA	CEA	CEA	CEA	CSPA	CEA
Drugs used for CEA and CSPA	**Group RF:** R 1 mg/ml + F 2 µg/ml **Group RFA:** same as in RF + A 2 µg/ml	**Group RF:** R 1.8 mg/ml + F 3 µg/ml **Group RFA:** same as in RF + A 4 µg/ml	**Group RF:** R 2 mg/ml + F 5 µg/ml **Group RFC:** same as in RF + C 2 µg/ml	**Group R:** R 2 mg/h **Group RM:** R 1 mg/h + M 8 µg/h	**All patients:** R 1.67 mg/ml + F 7.5 µg/ml
Bolus at beginning of CEA or CSPA	No	Yes (study infusion)	Yes (study infusion)	No	No[a]
Infusion rate	1 ml/10 kg/h (maximum 10 ml/h), intention to keep rate constant[b]	Initially 5 ml/h, later adjusted 3–8 ml/h	Initially 5 ml/h, later adjusted 3–7 ml/h	Initially 0.4 ml/h, later adjusted 0.1–0.4 ml/h	Initially 5 ml/h, later adjusted 3–10 ml/h
Top-ups during CEA or CSPA	No	Yes (study infusion)	No	No	Yes (study infusion)
Infusion scheduled	Until afternoon Day 2	Until 12:00 Day 2	Until 12:00 Day 1	For 24 h	At least until 11:00 Day 2
Follow-up until	Afternoon Day 2	12:00 Day 2	12:00 Day 1	48 h after catheter placement	Afternoon Day 2

CEA=Continuous epidural analgesia. CSPA=continuous spinal analgesia. R=Ropivacaine. F=Fentanyl. A=Adrenaline. C=Clonidine. M=Morphine. Day 1 and 2=First and second postoperative day, respectively. The adrenaline formula added to CEA in Studies I and II contained the preservatives sodium edetate and sodium metabisulphite (Adrenalin®, Leiras, Turku, Finland).

[a]However, 5 ml of ropivacaine 7.5 mg/ml were given as an epidural bolus at the end of surgery.
[b]However, reduced if pronounced hypotension or motor blockade.

The total amounts of epidurally administered drugs in Studies II–IV were calculated from those infusion rates marked on the patient's chart. The nurses had been instructed to be very diligent when recording the epidural infusion forms – kept bed-side – whenever infusion rate changes were

made. These data concerning infusion rates and time of infusion rate changes were entered to a spreadsheet application programmed by the author for this purpose (spreadsheet based on Microsoft® Excel 2002, Microsoft Corporation, Redmond, WA, USA).

Rescue pain medication

Table 12 summarizes data pertaining to additional regular pain medication and rescue pain medication. The first dose of propacetamol or paracetamol (acetaminophen) was given either together with the initiation of the continuous neuraxial infusion or already at the end of surgery (V). Furthermore, those patients who had knee replacement began receiving a NSAID in the evening following their operation. NSAIDs were considered contraindicated in the vascular surgery patients. The first-line rescue pain medication (Table 12) was either a bolus of the epidural infusion in Studies II and V or oxycodone given i.v. or i.m. in Studies I and III. If two successive doses failed to provide sufficient pain relief, the patients of Study II and V then received oxycodone i.v. or i.m. whereas those patients belonging to Studies I and III had an epidural bolus of ropivacaine as a second-line rescue drug. In Study IV, only oxycodone i.v. or i.m. was used as rescue medication.

Table 12. Additional and rescue pain medication.

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Additional regular medication					
Propacetamol[a] 2 g i.v.	Every 8 h for 24 h, then …	--	Single-dose, then …	--	--
Paracetamol[b] 1 g i.v.	--	Single-dose, then …	--	Every 8 h for 24 h, then …	Every 8 h until …
Paracetamol 1 g p.o.	… every 8 h	… every 8 h	… every 8 h	… every 8 h	… allowed to take p.o. every 8h
Rofecoxib[c] 25 mg p.o.	--	--	Every 12 h	--	--
Rofecoxib[c] 50 mg p.o.	--	Every 24 h	--	--	--
Celecoxib[d] 200 mg or diclofenac[e] 50 mg (p.o.)[f]	--	Every 12 h[f]	--	--	--
NSAID or tramadol (i.v. or p.o.)	--	--	--	--	On demand (maximally 3 times a day)
Rescue pain medication					
First-line	Oxycodone[g] i.v. or i.m.[h]	Bolus of epidural infusion	Oxycodone[g] i.v. or i.m.[h]	Oxycodone[g] i.v. or i.m.[h]	Bolus of epidural infusion
Second-line	Epidural bolus of ropivacaine	Oxycodone[g] i.v. or i.m.[h]	Epidural bolus of ropivacaine	--	Oxycodone[g] i.v. or i.m.[h]

[a]ProDafalgan®, Bristol-Myers Squibb.
[b]Perfalgan®, Bristol-Myers Squibb.
[c]Vioxx®, MSD.
[d]Celebra®, Pfizer.
[e]Voltaren®, Novartis.
[f]Instead of rofecoxib after the latter had been withdrawn in September 2004.
[g]Oxanest®, Leiras.
[h]Intravenous application in the postanaesthesia care unit and intramuscular on the ward.

Postoperative study parameters

Each study had its own study-specific follow-up chart. The study parameters and the assessment tools applied in each of the studies are shown in Table 13. The length of follow-up for each trial is listed in Table 11 while the times of postoperative interviews are displayed in Table 14. Study parameters were measured at least at each predetermined interview (Table 14) but additional recordings were made during routine nursing, particularly in case of any complaint and problem potentially related to postoperative pain treatment. When it came to statistical evaluation, data pertaining to blood pressure, heart rate, and respiratory rate were forwarded for analysis as measured at the predetermined interview. However, a different data handling was preferred with

Table 13. Study parameters after surgery.

	Comment
Study parameter	
Pain intensity	Evaluated at rest and during movement (*e.g.*, flexion of knee) on VAS graded from zero (no pain) to 10 (worst pain imaginable). VAS was 50 cm long (I, IV, and V) or 10 cm (II, III). Additionally, in Study V, pain assessed with modified PHH-score [Torda *et al.* 1995]: PHH-score 3=pain at rest PHH-score 2=pain during deep breathing PHH-score 1=pain on coughing PHH-score 0=no pain on coughing
Motor blockade	Assessed using modified Bromage scale [Bromage 1965]: 0=no motor blockade 1=just able to move knees 2=able to move feet only 3=unable to move feet or knees
Vital parameters	Blood pressure, heart rate, respiratory rate
Sedation	Evaluated as follows: 0=patient fully awake 1=patient tired or snoozes but easily wakes 2=patient sleeps or is drowsy but easily wakes 3= patient difficult to wake up
PONV	Assessed as follows: 0=no nausea or vomiting 1=nausea 2=retching or vomiting
Pruritus	Key: 0=none 1=slight to moderate 2=strong
Final interview	
Overall satisfaction	Overall satisfaction with pain management regimen estimated with one or more of the following: - Four-step verbal rating scale - Numerical rating scale from zero (worst) to ten (best) - "Would you choose the same kind of pain treatment for similar surgery in the future?" – yes/no/cannot say
Drowsiness	In Study III, at end of study: "Did you feel drowsy to a disturbing extent during the epidural study infusion?" (subjective estimate – yes/no/cannot say)
Prompt sequelae after CSA/CSPA	In Study IV: 48 hours after placement of spinal catheter, to record any possible prompt problems or complaints attributable to spinal catheter technique

VAS=Visual analogue scale. PHH-score=Modified Prince Henry Hospital pain score. PONV=Postoperative nausea and vomiting. CSA=Continuous spinal anaesthesia. CSPA=Continuous spinal postoperative analgesia.

respect to pain intensity at rest and during movement, satisfaction with pain treatment regimen, motor blockade, sedation, pruritus, as well as nausea and vomiting. Here, for each interval between two interviews, the highest or 'worst' value observed and recorded was passed on to data analysis although it may not have been one of the predetermined measurements.

Table 14. Time patterns of study parameter recording (interviews).

	Time pattern of interviews
Study I	First interview 6 h after start of CEA, next interviews at 09:00 and 14:00 both on Day 1 and 2
Study II	Interviews every hour for first three hours of epidural infusion, then at 18:00 Day 0, thereafter every six hours until 12:00 Day 2
Study III	First interview at 18:00 Day 0, thereafter interviews every 6 hours until 12:00 Day 1
Study IV	Interviews 4 and 8 hours after start of CSPA, next interview at 09:00 Day 1, and, finally, later on during Day 1 when spinal infusion was stopped
Study V	Patients observed in PACU several hours and until pain intensity was ≤3 on VAS. Interviews at 09:00 and 14:00 both on Day 1 and 2

CEA=Continuous epidural analgesia. Day 0=Day of surgery. Day 1 and 2=First and second postoperative day, respectively. CSPA=Continuous spinal postoperative analgesia. PACU=Postanaesthesia care unit. VAS=Visual analogous scale.

Treatment of bradycardia, hypotension, nausea and vomiting, and pruritus

Intraoperatively, glycopyrrolate i.v. or atropine sulphate i.v. were given for bradycardia. If hypotension occurred, this was treated by intravenous fluid challenge and, if necessary, with intravenous bolus doses of ephedrine. In Study I and IV, the first-line intraoperative vasopressor was intravenous phenylephrine while ephedrine i.v. was given if bradycardia accompanied hypotension.

Postoperatively, atropine sulphate i.v. was administered for bradycardia. Intravenous fluid challenge and boluses of ephedrine i.v. were given for hypotension (or phenylephrine i.v. in the PACU, Studies I and IV).

PONV was treated as required with a 5-HT_3 receptor antagonist i.v. combined, if necessary, with metoclopramide i.v. or with droperidol i.v. Pruritus was treated with oral hydroxyzine, as needed.

Study specific methods

Measurement of plasma drug concentrations (Study I)

Blood samples were collected into EDTA-tubes 6, 24, and 48 h after the start of the epidural infusion. The samples were centrifuged and the plasma stored at –20°C for determination of plasma concentrations of ropivacaine and fentanyl using high-performance liquid chromatography.

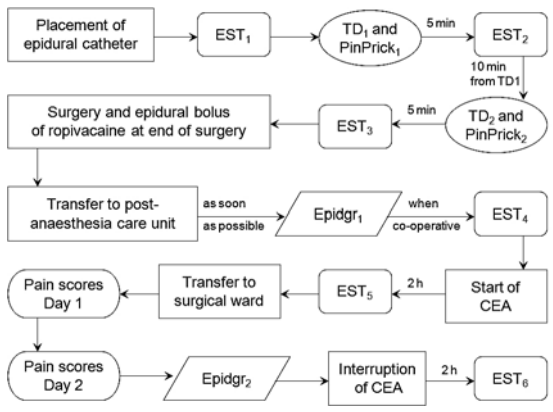
Ankle-brachial blood pressure index (ABPI) (Study I)

The ankle-brachial blood pressure index (ABPI) was measured preoperatively and in the morning of the first postoperative day in order to estimate whether the addition of adrenaline had an influence on the blood circulation of the lower extremities.

Methods used in Study V, including EST and epidurography

Some methods used in Study V varied from those in Studies I–IV and are, therefore, described in detail. Figure 1 gives an overview of the course of Study V including times when the various tests and measurements were performed ($EST_{1–6}$, $TD_{1–2}$, $PinPrick_{1–2}$, $Epidgr_{1–2}$, and measurement of pain scores). The epidural bolus of ropivacaine given at the end of surgery (Figure 1) consisted of 5 ml of ropivacaine 7.5 mg/ml. Figure 1 also shows when CEA was started in the PACU and when it was interrupted in relation to EST_6.

Figure 1. Flowchart giving an overview of the various tests and measurements performed during Study V.



EST=Epidural stimulation test. TD=Epidural test dose of 3 ml lidocaine 20 mg/ml with adrenaline 5 µg/ml. PinPrick=Evaluation of dermatomal spread of the sensory blockade with a pin-prick needle. Epidural bolus at end of surgery=5 ml of ropivacaine 7.5 mg/ml. Epidgr=Epidurography. CEA=Continuous epidural analgesia. Day 1 and 2=First and second postoperative day, respectively. Pain scores=Pain intensity rated in the morning and afternoon of Day 1 and in the morning of Day 2 utilizing a modified PHH-score (Table 13) followed by evaluation of maximum pain intensity on a VAS scale (Table 13).

Catheter placement (Study V)

After performing the LOR technique with physiological saline, a 19G epidural catheter (FlexTip Plus®, Epidural Catheterization Set, Arrow International Inc., Reading, USA) was advanced 4 cm beyond the tip of the Tuohy needle. The SnapLock® catheter adapter, a Johans ECG adapter® (Arrow International Inc.), a 3-way stop cock, and a bacterial filter were attached to the catheter in this order.

EST (Study V)

Supervised hands-on training in the EST technique preceded Study V. EST was performed utilizing similar equipment and according to the method described by Tsui and colleagues [Tsui *et al.* 1998]. These included the metal coil reinforced epidural catheter FlexTip Plus®, the Johans ECG adapter®,

and the nerve stimulator Dakmed model 750 digital® (Dakmed Inc., Buffalo, USA). Briefly, the electrical impulse (1 Hz, 0.2 sec) was gradually increased from zero to maximally 16 mA or until muscle twitching became observable. The position of the epidural catheter tip was then assessed as follows [Tsui *et al.* 1998]:

a) within the epidural space, if truncal or lower limb motor response occurs at 1–10 mA;

b) outside the spinal canal if motor response is first seen at a current >10 mA, or is absent;

c) intrathecally or directly against a nerve root if a motor response is manifested at <1 mA. Here, a polymyotome twitching would indicate an intrathecal position whereas a unilateral, segmental response combined with a negative aspiration test for CSF should suggest that the catheter tip lies directly on a nerve root (but not intrathecally).

The current applied at the onset of myotomal activity (motor response threshold) was recorded, as was the level at which the patients first felt the electrical stimulation (sensory response threshold). In each patient, EST was repeated six times ($EST_{1–6}$) (Figure 1). The motor response was divided to one of the following categories [Goobie *et al.* 2003]: *Category T1–6* (intercostal muscle), *Category T7–12* (rectus abdominus and external oblique muscle), or *Category L1-5* (hip flexion). Before EST_1, the catheter-adapter assembly was primed with physiological saline 1–2 ml. If the electrical circuit during EST was interrupted then the system was flushed with small amounts of physiological saline.

Epidural test dose and pin-prick (Study V)

After EST_1, with the patient remaining in the sitting position or in the lateral decubitus position, the first epidural test dose (TD_1) was given (Figure 1). The patient was then turned into the supine position. Three minutes after TD_1, the dermatomal spread of sensory blockade was tested using a pin-prick needle ($PinPrick_1$). At 5 minutes from TD_1, EST_2 was performed, and at 10 minutes, a second analogous test dose (TD_2) was given (Figure 1). The spread of sensory block was tested again ($PinPrick_2$) and EST_3 performed 3 and 5 min after EST_2, respectively (Figure 1).

Epidurography (Study V)

The initial epidurography ($Epidgr_1$, anteroposterior view) was taken on the patient's arrival in PACU, and the second ($Epidgr_2$, anteroposterior and lateral view) was performed at 11:00 on Day 2 (Figure 1). The contrast media, either 5ml iohexol 240 I/ml (Omnipaque®, GE Healthcare) or ioversol 240 I/ml (Optiray®, TYCO), was injected through the side port of the 3-way stop cock under strict aseptic conditions.

Statistics

Descriptive statistics were used in all five studies. The groups were compared with chi-square test (χ^2 test) or Fisher's exact test for categorical data, with *t*-test or two-way repeated-measures analysis of variance (RM ANOVA) for continuous, normally distributed data, and with the Mann-Whitney *U* test (MW-*U*) for non-parametric data (I–IV). For example, VAS scores were analyzed with the MW-*U* and changes in motor response thresholds over time (EST_{1-6}, Study V) with the two-way RM ANOVA. As appropriate, 95% confidence intervals (95% CI) were calculated. A *p*-value (*p*) <0.05 was taken as being statistically significant.

Statistical calculations were performed using the SigmaStat® for Windows® computer program (Version 2.03, SPSS Inc., Chicago, IL, USA) (I) or the StatView® for Windows® computer program (Version 5.0.1., SAS Institute Inc., Cary, NC, USA) (II–V). Where appropriate, 95% CI for

population medians were computed with the software Confidence Interval Analysis (Version 2.1.1, by Bryant TN, University of Southampton, UK, 2000).

Power analysis

For Studies I–IV, a power analysis was performed based on a significance level α=0.05, a power of 80%, and a two-sided (I–III) or one-sided (IV) test.

Study I

The estimation of the sample size was based on previously published data [Niemi and Breivik 1998]. A 40% reduction of VAS pain scores was taken as being clinically relevant in the study patients, *i.e.*, a reduction from 50 mm to 30 mm on a 100-mm VAS scale with a standard deviation of 25 mm; thus, the estimated sample size was 25 patients in each group.

Study II

As no epidural analgesia studies with similar adrenaline containing drug mixtures in patients after TKA were available, the sample size calculation was based on historical data [Silvasti and Pitkänen 2001; Förster and Rosenberg 2004]. With an average rescue requirement of 16 mg oxycodone i.m. (SD 11 mg) and assuming a mean reduction of 50% as being clinically significant, 31 patients/group were found necessary to detect statistical significance. In order to allow for possible drop-outs, a total of 35 patients were allocated to each group.

Study III

Sample size was calculated based on estimations of the primary end point, *i.e.*, the amount of the rescue medication (oxycodone i.m.): Using previous experience (mean 11 mg, SD 8 mg) and assuming a mean reduction of 50% (5.5 mg) as clinically significant, 34 patients/group were considered necessary to detect statistical significance.

Study IV

A total of 20 patients per group were considered necessary to detect statistical significance based on previous experience with bupivacaine [Bachmann *et al.* 1997]: mean difference between the groups 23% when comparing CSPA with bupivacaine 2 mg/h alone *versus* bupivacaine 1 mg/h and morphine 8 µg/h with respect to the number of patients scoring a modified Bromage score of 2 or 3. The latter study was used as basis for the power analysis due to lack of available comparative data for ropivacaine with CSPA. To allow for possible drop-outs, 23 patients were allocated to each group.

Results

Patients and surgery

Patients enrolled, randomized, and analysed

Altogether, 269 patients were entered into the Studies I–V during 2001–2006. Of these, 239 patients were enrolled into the randomized Studies I–IV, and 30 others to the diagnostic Study V. In one patient belonging to Study IV, the identification of the intrathecal space failed at lumbar puncture (Table 15). This patient was replaced by the next recruited patient with regard to the randomization code which still was sealed at that time. The remaining 238 patients were randomized in Studies I–IV as shown in Table 15. In addition, this table provides an overview of reasons why 16 of these 238 patients were excluded from data analysis (total drop-outs). The patients who withdrew their consent during the course of the study (Table 15) did not do so because of possible adverse outcomes or clinically significant side-effects, but rather because they preferred to be no longer bound by the study protocol. One patient (Study II, Group RF) received, due to human error, an epidural drug infusion with a higher than intended fentanyl concentration. Despite the higher fentanyl concentration (6 μg/ml), this patient did well and showed no obvious opioid related side-effects except itching on his chest. He was withdrawn from the study when the error was recognized during the stay at the PACU.

The data of 222 of the 238 randomized patients were analyzed (I–IV) (Table 15). These 222 patients were divided into 178 patients having had CEA (I–III), and 44 others who received CSPA (IV). Of the former group, 24 patients (Table 15) dropped out of the study later. Their data were, nevertheless, included in the statistical analysis until the time of their withdrawal. The reasons for being withdrawn prematurely included technical problems (*n*=5), postoperative confusion (*n*=4; in two of these individuals, postoperative confusion led to catheter dislodgment), accidental catheter dislodgment (*n*=2), and insufficient pain relief (*n*=2). The time points of premature withdrawals are specified for each individual in the original publications (Table 2 in Study I; Table 1 in Study II; Table 1 in Study III). All 44 patients who entered the CSPA part of Study IV completed it.

In Study V, 25 of the 30 patients received CEA. In two of these 25 patients receiving CEA, the catheter became accidentally dislodged. In the remaining five patients of Study V, the catheter was located either not within the spinal canal (*n*=4) or intrathecally (*n*=1). Despite these unwanted outcomes (paravertebral and intrathecal catheter position; premature catheter dislodgment), all 30 patients were included in the analysis with respect to EST (Study V) and data synthesis of Studies I–V.

Table 16 summarizes numbers of patients involved in Studies I–V.

Demographic data and premedication

Demographic data are shown in Table 17. Patients undergoing arterial bypass surgery (I and IV) were on average slightly older than those who underwent knee replacement (II and III). Regarding the body mass index (BMI), there was a reversed trend with more obese patients being in Studies II and III (mean 28 kg/m^2) as compared to patients in Studies I and IV (mean 25 kg/m^2) (Table 17). Patients younger than 40 years (arbitrary cut-off) were found only in Study V (five patients). The overall distribution for physical status was as follows: ASA class I *n*=18, ASA class II *n*=65, ASA

class III *n*=162, and ASA class IV *n*=7. Patients in Studies I and IV were on average in a worse condition of health than patients in Studies II–III and V based upon ASA class data (Table 17).

Treatment groups and control groups did not statistically differ from each other as regards patient characteristics and premedication within each Study I–IV (Table 17) except that patients in Group RFA were heavier and received higher doses of the premedication drug than those in Group RF in Study I (Table 17).

Table 15. Number of patients enrolled, randomized, and forwarded to statistical analysis in the randomized, controlled, and double-blinded studies (I–IV).

	Study I		*Study II*		*Study III*		*Study IV*		*Total Studies I–III*	*Total Studies I–IV*
Enrolled	50		70		72		47		192	239
Failure to identify intrathecal space	–		–		–		1		–	1
Group	*RFA*	*RF*	*RFA*	*RF*	*RFC*	*RF*	*RM*	*R*		
Randomized	25	25	35	35	36	36	23	23	192	238
Total drop-out	4	–	4	3	–	3	1	1	14	16
- Failure of continuous neuraxial analgesia	2	–	4	2	–	1	–	–	9	9
- Withdrawal of consent	1	–	–	–	–	1	1	–	2	3
- Inadvertent protocol violation	–	–	–	1[a]	–	1[b]	–	–	2	2
- Others	1[c]	–	–	–	–	–	–	1[d]	1	2
Forwarded to statistical analysis	21	25	31	32	36	33	22	22	178	222
Drop-out during continuous postoperative neuraxial analgesia	1	8	6	4	3	2	–	–	24	24

Data are numbers of patients. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine. RM=Spinal infusion of ropivacaine and morphine. R=Spinal infusion of ropivacaine alone.

[a]Wrong epidural drug mixture.
[b]Protocol violation concerning the epidural infusion regimen.
[c]Signs of myocardial ischaemia and acute moderate heart insufficiency, treated with various drugs including repeated i.v. opioid. Patient recovered without detectable increase of cardiac enzymes.
[d]Conversion to general anaesthesia.

Table 16. Summary regarding number of patients involved in Studies I–V.

	No. of patients	*Comment*
Enrolled	269	Studies I–V
Randomized	238	Studies I–IV
Without randomization	30	Study V
Disposed to puncture of epidural space and application of catheter	222	192 patients Studies I–III + 30 patients Study V
CEA started	217	192 patients Study I–III + 25 patients Study V
Disposed to puncture of intrathecal space with intention to place spinal catheter	47	Study IV
Successful application of spinal catheter followed by CSA for surgery	46	Study IV
Administration of CSPA	44	Study IV
Forwarded to detailed analysis	252	178 patients Studies I–III + 44 patients Study IV + 30 patients Study V

CEA=Continuous epidural analgesia. CSA=Continuous spinal anaesthesia. CSPA=Continuous spinal postoperative analgesia.

Table 17. Demographic data and premedication.

	Study I		*Study II*		*Study III*		*Study IV*		*Study V*
Group	RFA	RF	RFA	RF	RFC	RF	RM	R	
No. of patients	21	25	31	32	36	33	22	22	30
Gender (female/male)	6/15	12/13	25/6	22/10	24/12	23/10	10/12	11/11	14/16
Age (years)	70 (9) (51–81)	71 (13) (41–88)	67 (11) (46–85)	69 (9) (42–82)	70 (9) (43–83)	68 (11) (38–82)	72 (10) (51–94)	72 (11) (51–95)	57 (17) (19–82)
Weight (kg)	76 (13)	67 (12)*	76 (13)	77 (13)	76 (14)	81 (17)	74 (15)	68 (14)	74 (16)
Height (cm)	172 (9)	167 (8)	166 (9)	167 (10)	166 (10)	167 (11)	171 (7)	165 (11)	171 (8)
BMI (kg/m^2)	26 (3.5)	24 (3.5)	28 (3.9)	28 (3.2)	27 (4.1)	29 (3.8)	25 (4.7)	25 (4.7)	25 (4.1)
ASA class (I/II/III/IV)	NA/0/21/0	NA/0/22/3	7/7/17/NA	4/11/17/NA	0/13/23/NA	3/13/17/NA	NA/1/21/0	NA/0/18/4	4/20/6/0
Premedication p.o. diazepam (mg)	10 (6.9/10)	7.5 (5/8.1)[#]	15 (10/15)	15 (10/15)	7.5 (5/10)	10 (5.7/10)[§]	8.8 (5/10)	7.5 (5/10)	10 (10/10)

Data are number of patients, mean (SD), or median (25^{th}/75^{th} percentiles). For age data are mean (SD) (range). RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine. RM=Spinal infusion of ropivacaine and morphine. R=Spinal infusion of ropivacaine alone. BMI=Body mass index. ASA class=American Society of Anesthesiologists physical status classification. NA=Not applicable.

*p=0.027, t-test.
[#]p=0.017, MW-U test.
[§]p=0.6, MW-U test.

Surgery

Relevant surgery data are summarized in Table 18 (I and IV) and Table 19 (II and III). The surgical procedures performed in Study V were thoracotomy (*n*=4), upper abdominal (*n*=4), and lower abdominal (*n*=22).

Table 18. Surgery related results pertaining to Studies I and IV.

	Study I		*Study IV*	
Group	*RFA*	*RF*	*RM*	*R*
Duration of surgery (min)	171 (67) (101–375)	187 (82) (90–434)	164 (66–299)	182 (89–327)
Duration ≥3 h (no.)	8	15	9	11
Type of bypass				
Vein (no.)	13	22	7	8
Prosthesis (no.)	8	3	15	14

Data are mean (SD) (range) or number of patients. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. RM=Spinal infusion of ropivacaine and morphine. R=Spinal infusion of ropivacaine alone.

Table 19. Surgery related results pertaining to Studies II and III.

	Study II		*Study III*	
Group	*RFA*	*RF*	*RFC*	*RF*
Duration of surgery (min)	121 (26)	122 (27)	89 (28)	98 (21)
Tourniquet				
Duration (min)	101 (22)	101 (19)	77 (20)	86 (17)
Pressure (mmHg)	250 (250–300)	250 (250–300)	320 (300–350)	320 (300–360)

Data are mean (SD) or median (range). RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine.

Anaesthesia and intraoperative data

Anaesthesia

All surgical procedures were successfully performed under the planned regional anaesthesia technique planned, *i.e.*, SSA together with epidural top-ups, when needed, in Studies I–III and CSA in Study IV (except one conversion to GA, Table 15). Study and control groups did not differ in a statistically significant way regarding the number of epidural top-ups given intraoperatively in Studies I–III (*e.g.*, 6 top-ups in Group RF and 1 top-up in Group RFA in Study II; p=0.1, Fisher's exact test). However, in Study IV, patients from Group RM received higher amounts of intrathecal ropivacaine during surgery as compared to Group R despite comparable duration of surgery: median (range) 34 (18.8–41.3) mg *versus* 23 (15.0–41.3) mg. This difference achieved statistical significance (p=0.03, MW-U) with a median difference of 7.5 (95% CI 0–11.3) mg. Apart from the latter difference, treatment and control groups were comparable within Studies I–IV with regard to other intraoperative parameters, such as sedatives, vasoactive drugs, and the time interval from spinal anaesthesia being done to start of the continuous neuraxial analgesia.

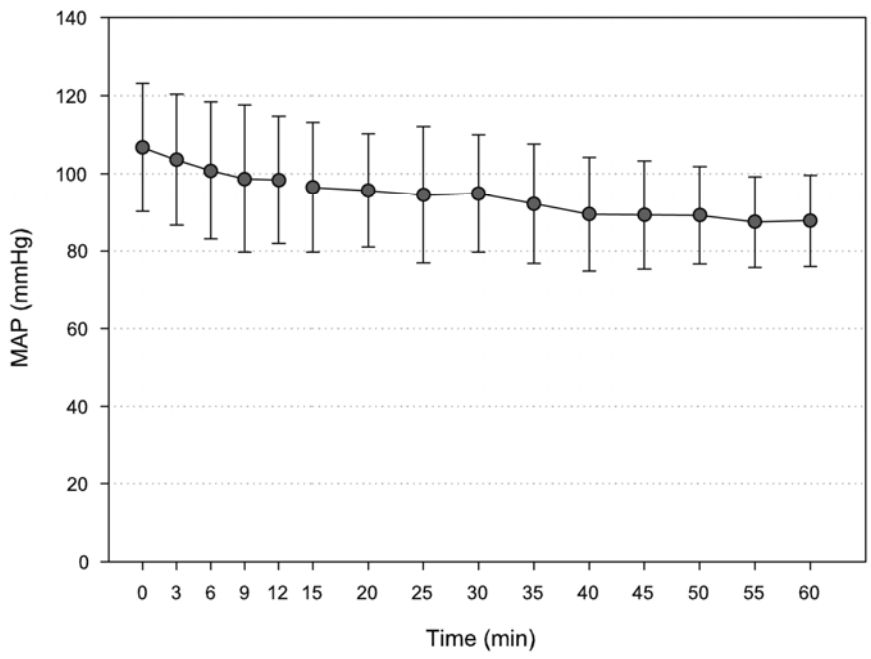
Spinal anaesthesia spread slowly in Study IV; hypoaesthesia to cold was found at the T9–T10 level after 20 (range 15–25) min (no difference between groups). Because of the slow spread, slight head-up tilt of the operating table was made in five patients. Thirteen patients experienced mild pain during skin incision (no inter-group difference) and were treated with fentanyl i.v. (11 patients), intrathecal top-ups (12 patients), and with local infiltration of lidocaine 10 mg/ml (4 patients).

In Study I, 26 of 45 patients had epidural top-ups after SSA, while in Study IV, 26 of 44 patients received intrathecal top-ups after the first hour of CSA. In Study IV, as the operation neared its completion, 3 patients although still maintaining an adequate sensory block, moved their legs to such an extent that it disturbed the surgeons.

Haemodynamics during first hour (Study IV)

Mean arterial blood pressure (Figure 2), CVP, and heart rate decreased slightly during the first hour after starting CSA (for all parameters $p<0.0001$, RM ANOVA). During the first hour of CSA, four patients received phenylephrine i.v. for hypotension with the total doses being less than 0.2 mg. Mean CVP values were 4–7 mmHg throughout the initial 60 min observation period.

Figure 2. Mean arterial blood pressure (MAP) during first 60 min into CSA (IV).



CSA=Continuous spinal anaesthesia. Data originate from the 44 patients who received continuous spinal postoperative analgesia (CSPA) in Study IV. Symbols are mean and SD. Open circles are absolute lowest MAP observed at each time point. The decrease in MAP over time was statistically significant ($p<0.0001$, $F>25$, RM ANOVA).

Anaesthesia for revision surgery (Study IV)

On four occasions in Study IV, surgical revision became necessary early in the postoperative phase because of wound haematoma formation (1 in Group RM, 3 in Group R). CSPA was thus interrupted and increments of 0.5–1.0 ml of ropivacaine 7.5 mg/ml were given through the spinal

catheter to establish surgical anaesthesia. The interventions lasted 20–60 min and CSPA was again started when voluntary contractions of the thigh muscles were seen.

Postoperative pain relief

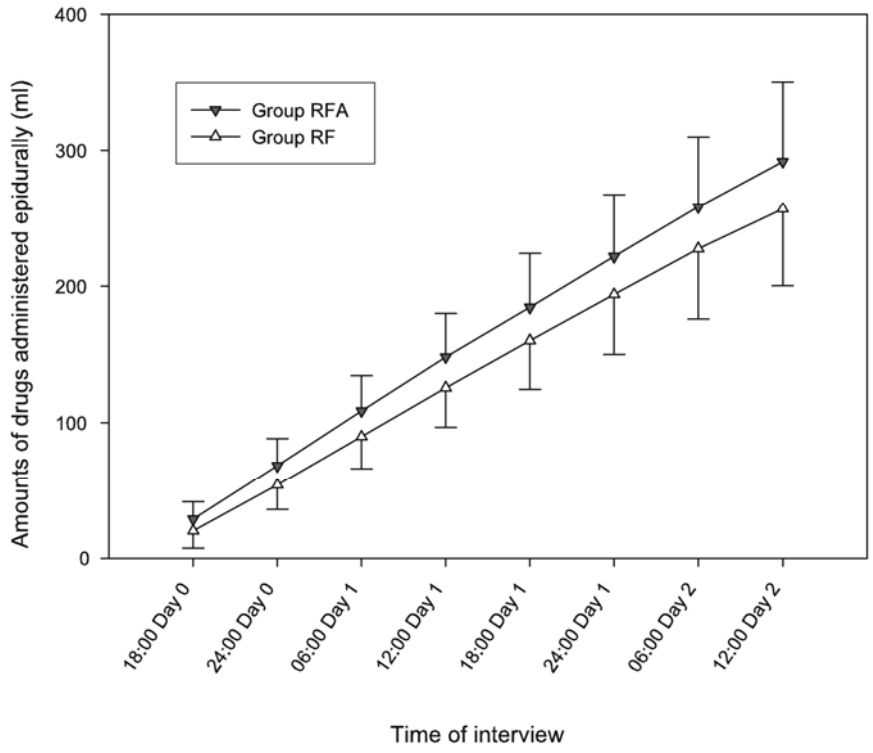
Failure of CEA or insufficient CEA occurred in nine of the 192 patients (5%) in Studies I–III. CEA produced adequate pain relief in all 25 patients of Study V in whom epidurography showed the tip of the catheter in the epidural space. Analgesia was adequate in all CSPA patients in Study IV.

Postoperative analgesia in Studies I–V

Study I

In Study I, the VAS pain values at rest and on movement did not differ significantly between the two groups at any of the observation times. Furthermore, the addition of adrenaline to the infusion had no effect on the need for rescue medication. The mean (SD) oxycodone i.m. consumption over 48 h was 3.3 (5.2) mg in seven patients belonging to Group RFA as compared to 3.7 (5.4) mg in nine patients belonging to Group RF (not significant).

Figure 3. Amounts of infusion administered epidurally during CEA in Study II.



CEA=Continuous epidural analgesia. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. Day 0=Day of surgery. Day 1 and 2=First and second postoperative day, respectively. Symbols are mean with SD. The two factors group and time were connected with each other in a statistically significant way (p=0.02, F=2.4, two-way RM ANOVA).

Study II

In Study II, a significantly higher amount of the epidural infusion was administered in Group RFA as compared to Group RF (Figure 3). The difference between the groups was statistically significant at each interview time with mean (SD) cumulative amounts being 283 (68) ml in Group RFA and 243 (70) ml in Group RF (mean difference 40 (95% CI 5–75) ml; p=0.025, t-test). The period from the start of the epidural infusion to the first interview at 18:00 Day 0 was somewhat longer in Group RFA than in Group RF; this difference, however, did not reach statistical significance (Table 20).

The total amounts or number of doses of oxycodone i.v. and i.m. were similar in both groups of Study II; as were the combined number of i.v. and i.m. oxycodone doses and epidural boluses (Table 20). Median VAS pain scores were ≤3 at rest at all time points, except in RFA at 24:00 Day 0 (Figure 4). There was a statistically significant difference between the groups regarding pain scores when moving at 24:00 Day 0 and at 06:00 Day 2, when higher values were seen in Group RFA (Figure 4).

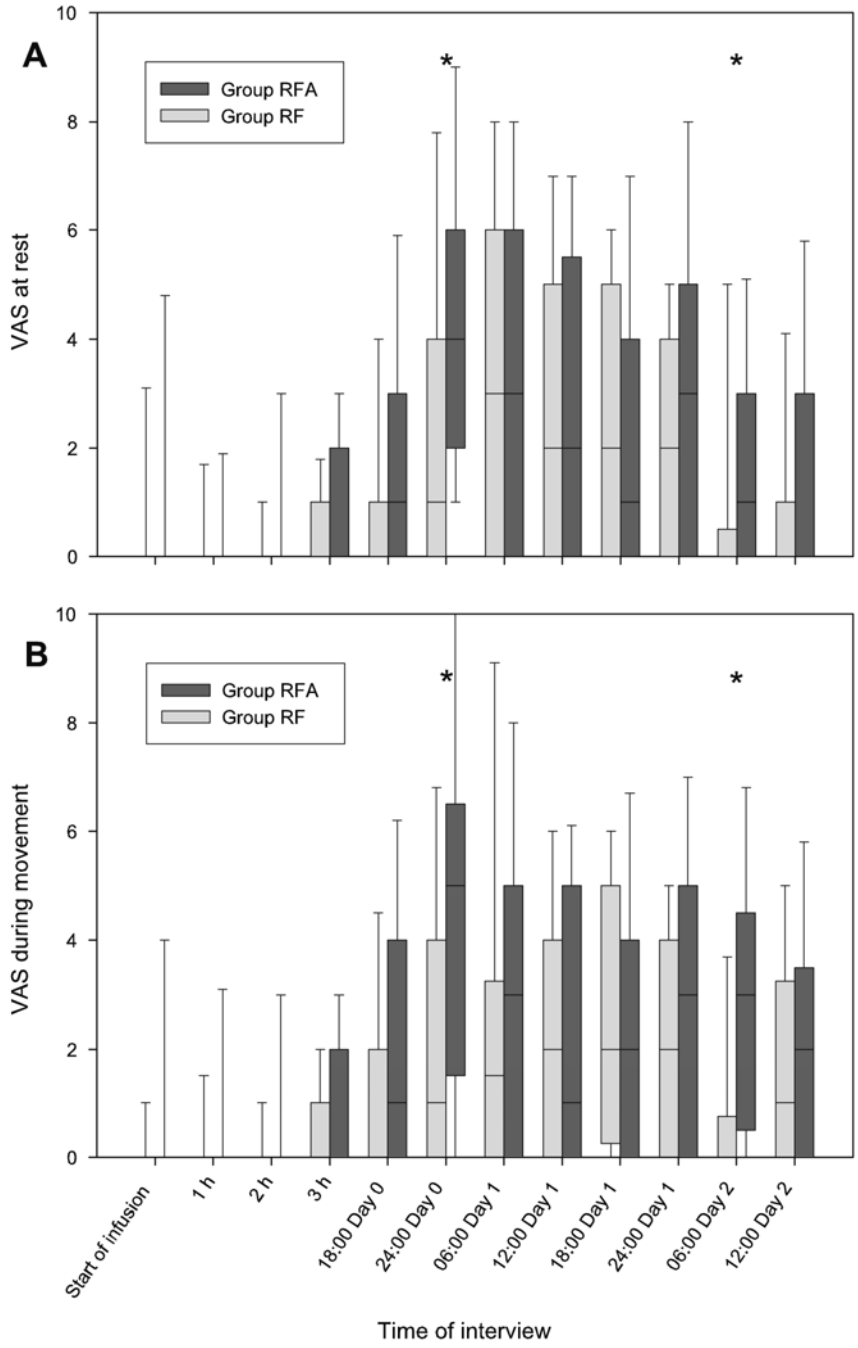
Table 20. Results related to pain management during CEA in Study II.

	Group RFA	*Group RF*	*p-value*
Time from spinal anaesthesia to start of epidural infusion (min)	216 (33)	222 (56)	
Time from start of epidural infusion to 18:00 Day 0 (min)	297 (91)	244 (56)	0.06 (*t*-test)
Epidural boluses given postoperatively (no.)	3 (1/5)	2 (0.5/3)	0.2 (MW-*U*)
Sum of postoperative oxycodone doses i.v. and i.m. (no.)	1 (0/3)	0 (0/1.5)	0.07 (MW-*U*)
Sum of postoperative epidural boluses and oxycodone doses (no.)	6 (1.3/8)	3 (1/5)	0.11 (MW-*U*)
VAS pain scores ≤3 at rest (yes/no) (no. of patients)			
Until 12:00 Day 1	5/26	9/23	
Until 12:00 Day 2	4/27	7/25	
Separate breakthrough pain episodes (no.)			
VAS pain score at rest 4–6	3 (1/4)	1.5 (1/3)	
VAS pain score at rest 7–10	0 (0/2)	0 (0/1)	
Patients' satisfaction (no. of patients)[a]			
18:00 Day 0	21/4/5/1	17/12/0/0	0.02 (χ^2 test)
24:00 Day 0	10/7/6/5	12/15/1/2	0.048 (χ^2 test)
Patients' overall satisfaction with pain management regimen[b]	9 (8/10)	9 (9/10)	0.12 (MW-*U*)

Data are mean (SD), median (25^{th}/75^{th} percentiles), or number of patients or observations. CEA=Continuous epidural analgesia. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. Day 0=Day of surgery. Day 1 and 2=First and second postoperative day, respectively. VAS=Visual analogues scale.

[a]Key for patients' satisfaction with pain treatment: very satisfied / satisfied / cannot say / not satisfied.
[b]Patients' overall satisfaction estimated on a numerical rating scale from zero (worst) to ten (best).

Figure 4. VAS pain scores at rest (A) and during movement (B) in Study II.

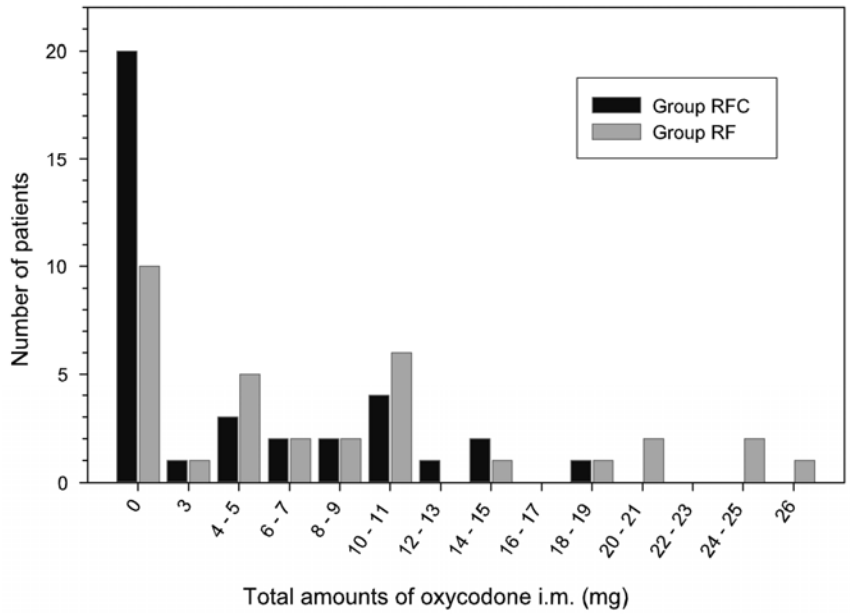


Box plots are medium with 25th/75th percentiles; whiskers are 10th/90th percentiles. VAS=Visual analogues scale. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RF=Epidural infusion of ropivacaine and fentanyl. Day 0=Day of surgery. Day 1 and 2=First and second postoperative day, respectively. *p-values 0.03–0.003, MW-U.

Study III

In Study III, patients of Group RFC received a significantly smaller amount of the epidural drug infusion as compared to Group RF (p=0.01, F=6.49, RM ANOVA). The difference between the groups was statistically significant at each interview time beginning at 24:00 Day 0. The mean (SD) cumulative amounts of infused drugs were 100 (17) ml in Group RFC and 113 (20) ml in Group RF (mean difference 13 (95% CI 4–22) ml; p=0.025, t-test).

Figure 5. Total amounts of intramuscular oxycodone given postoperatively during Study III.



RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine. RF=Epidural infusion of ropivacaine and fentanyl.

At the same time, patients of Group RFC received less intramuscular oxycodone (Figure 5) with a median amount (25^{th}/75^{th} percentiles) of 0 (0/7) mg in RFC, as compared to 7 (0/12) mg in RF. This difference achieved statistical significance (p=0.027, MW-U) with a median difference of 3 (95% CI 0–7) mg. One patient in Group RFC received an epidural bolus of ropivacaine as additional medication when compared to three patients of Group RF who received six doses of ropivacaine. Other parameters related to pain management during CEA in Study III are summarized in Table 21. VAS pain scores at rest and during movement did not differ statistically at any interview point except at 24:00, when lower pain scores were observed in RFC (p<0.025, MW-U).

Table 21. Results related to pain management during CEA in Study III.

	Group RFC	*Group RF*
VAS pain scores ≤3 at rest until 12:00 Day 1 (yes/no) (no. of patients)	15/21	6/27
Separate breakthrough pain episodes (no.)		
VAS pain score at rest 4–6	32 (17 patients)	49 (21 patients)
VAS pain score at rest 7–10	13 (8 patients)	31 (17 patients)
Patients receiving oxycodone i.m. (yes/no) (no.)	16/20	23/10*
Patients' overall satisfaction with pain management regimen[a]	9 (8/10)	8 (5.8/10)[#]

Data are number of patients or observations, or median (25^{th}/75^{th} percentiles). CEA=Continuous epidural analgesia. RFC=Mixture of ropivacaine, fentanyl, and clonidine. RF=Mixture of ropivacaine and fentanyl. Day 1=First postoperative day. VAS=Visual analogues scale.

[a]Patients' overall satisfaction estimated on a numerical rating scale from zero (worst) to ten (best).
*p=0.06, χ^2 test
[#]p=0.08, MW-U

Study IV

In Study IV during CSPA, on average, a larger volume of the study drug infusion was given intrathecally in Group RM as compared to Group R: median (25^{th}/75^{th} percentiles) 8.8 (8.4/9.0) ml *versus* 8.4 (8.1/8.7) ml (p=0.03, MW-U, median difference 0.4 (95% CI 0.04–0.7) ml). Pain relief was comparable in both groups as noted by VAS pain scores at rest and during movement. The consumption of oxycodone rescue medication did not differ significantly between Groups RM and R with median (25^{th}/75^{th} percentiles) numbers of oxycodone doses of 3 (1/7) and 5 (3/8), respectively (p=0.12, MW-U). No oxycodone was needed in the study period in 5 patients from Group RM and 11 others from Group R (p=0.12, χ^2 test with Yates' continuity correction). After discontinuing the spinal infusion on the first postoperative day, three patients from each of these groups did not get any oxycodone during the following 24 hours.

Study V

In Study V, there was adequate pain relief in all 25 patients given CEA. Two of these 25 individuals developed asymmetric and insufficient epidural analgesia which was successfully treated with epidural top-ups. The median (25^{th}/75^{th} percentiles) number of epidural boluses given on the surgical ward was 0 (0/1). On the surgical ward, a single patient needed rescue oxycodone i.m. The median (25^{th}/75^{th} percentiles) PHH-scores were 1 (0/3), 1 (1/3), and 1 (0/2) on the morning and afternoon of Day 1 and on the morning of Day 2, respectively. Correspondingly, the highest VAS pain scores were 2 (0/3.3), 3 (1/3.3), and 2 (0/2).

Patients' satisfaction with pain management

There were no significant inter-group differences regarding the patients' satisfaction with the pain treatment as determined by the interviews in Studies I–IV except for patients in Study II whose satisfaction was significantly higher in Group RF as compared to Group RFA on the first evening and during the first night after surgery (Table 20).

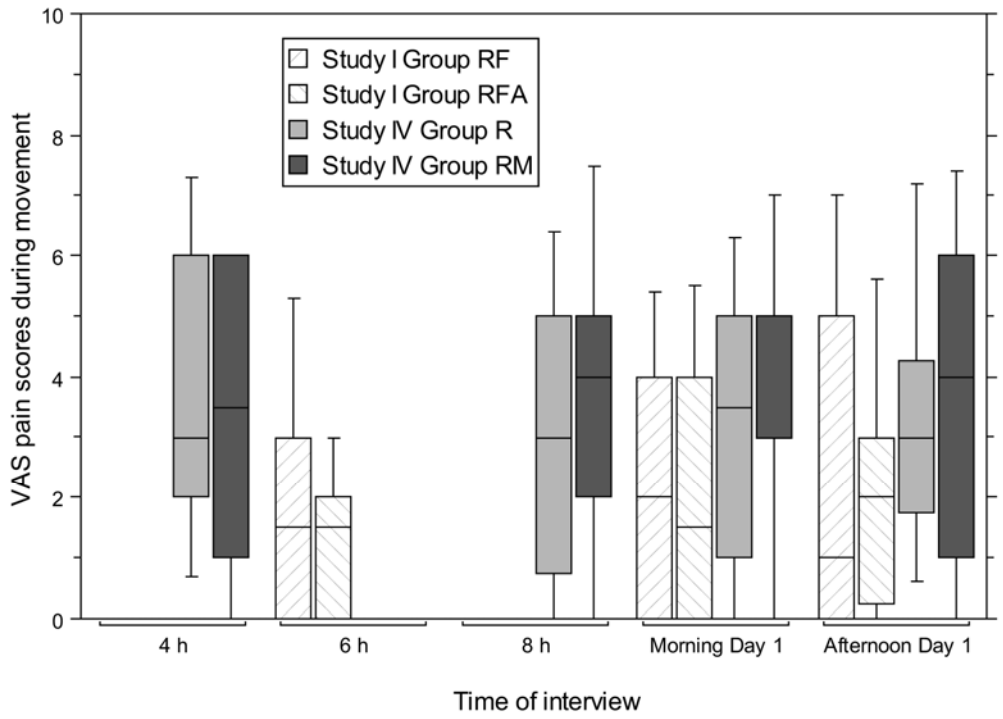
Data pertaining to overall satisfaction with the pain management regimen noted at the end of Studies II and III are presented in Table 20 and Table 21 with no statistical differences noted between the groups.

Comparison of Studies I and IV and of Studies II and III

Study I versus Study IV

Examining the VAS scores experienced by moving in Studies I and IV during the first 24 hours, there seemed to be a trend towards higher pain levels with CSPA when compared to CEA (Figure 6). However, the patients' overall satisfaction with pain treatment was good to excellent in both studies (Table 3 in Study I and Table 4 in Study IV). The low VAS pain scores at rest in Studies I and IV demonstrated no difference between the two trials.

Figure 6. VAS pain scores during movement acquired in Studies I and IV during the first 24 hours after surgery.



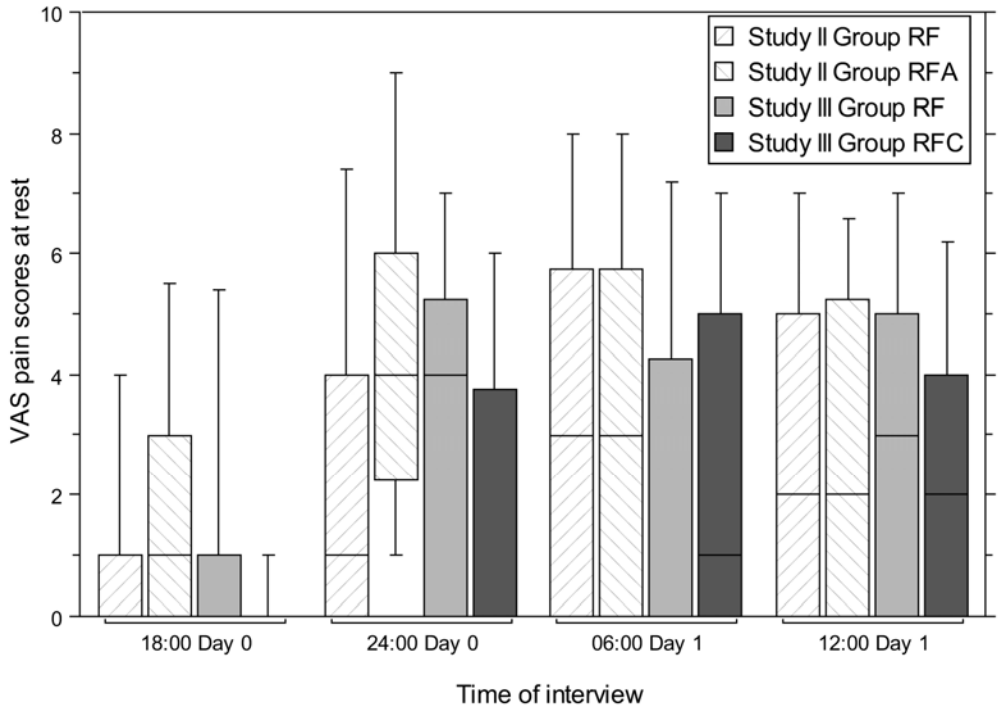
VAS=Visual analogue scale. RF=Epidural infusion of ropivacaine and fentanyl. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. R=Spinal infusion of ropivacaine alone. RM=Spinal infusion of ropivacaine and morphine. Day 0=Day of surgery. Day 1= First postoperative day.

Study II versus Study III

The VAS pain scores from Studies II and III acquired during the first four interviews performed at 6-hours intervals revealed no clear pattern as to which pain relief was preferable (Figure 7 and Figure 8). However, the pain scores in Group RFA of Study II tended to be higher and those of Group RFC of Study III lower on the first evening and night after surgery.

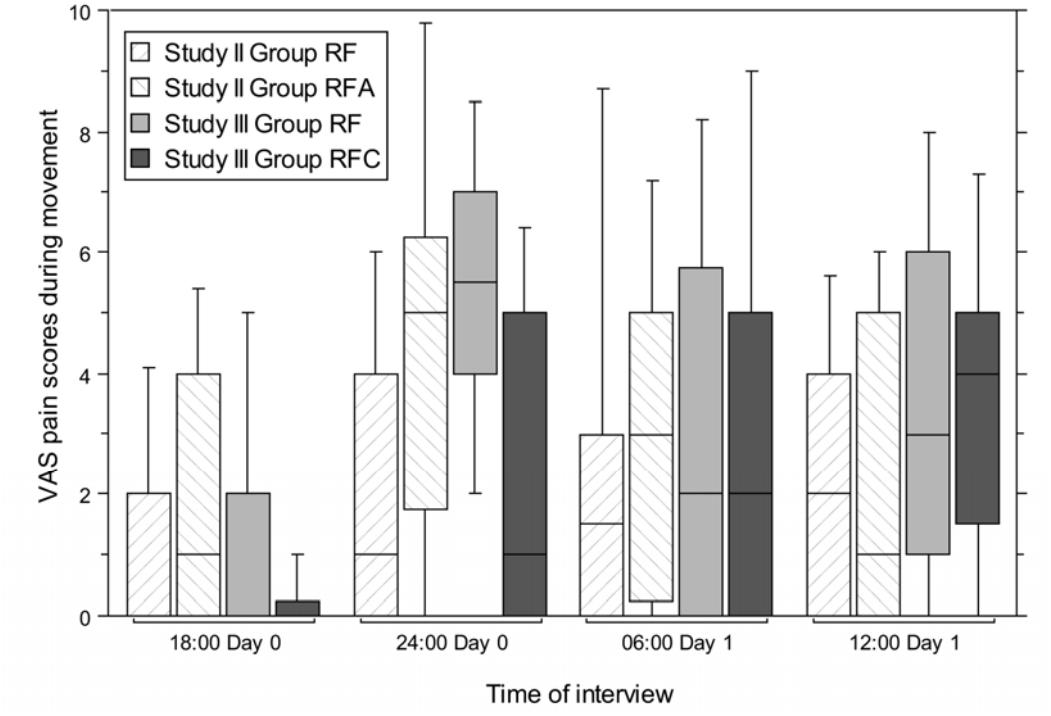
Regarding the patients' overall satisfaction with the management of pain, no difference was found between Study II and Study III (Table 20 and Table 21).

Figure 7. VAS pain scores at rest in Studies II and III at the first four interviews performed at 6-hour intervals.



VAS=Visual analogues scale. RF=Epidural infusion of ropivacaine and fentanyl. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine. Day 0=Day of surgery. Day 1= First postoperative day.

Figure 8. *VAS pain scores during movement in Studies II and III at the first four interviews performed at 6-hour intervals.*



VAS=Visual analogues scale. RF=Epidural infusion of ropivacaine and fentanyl. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. RFC=Epidural infusion of ropivacaine, fentanyl, and clonidine. Day 0=Day of surgery. Day 1= First postoperative day.

Side-effects and complications

No serious side-effects or complications with persistent sequelae were observed in any of the Studies I–V.

Sedation

Generally, the degree of sedation was low in all Studies I–V. Sedation of grade 3 was registered once in both Study I (Group RF) and Study II (Group RF), and twice in Study III (one individual in each Group RF and RFC). Vital signs, including respiratory rate, were stable at these points of time and the patients scored only low sedation grades thereafter. Additionally, one patient from Group RM in Study IV once scored sedation of grade 3. This happened in the PACU, 8 h after the start of CSPA and shortly after the patient had received haloperidol 5 mg i.v. for restlessness and confusion.

In Study III, the addition of clonidine did not increase the sedation scores in Group RFC as compared to RF. One-third of all patients belonging to Study III felt ‘drowsy to a disturbing extent’ at some point during CEA (Table 13) with no inter-group statistical difference being observed.

Paraesthesia, bloody tap, neurological symptoms

In Study IV, 11 of 46 patients experienced short lasting, mild paraesthesia during lumbar puncture or while advancing the catheter. A bloody tap occurred during lumbar puncture in three patients of Study IV, however, once free flow of CSF was obtained, the macroscopic appearance of the latter was clear on all occasions.

The one patient from Study V, in whom dura perforation at a thoracic level occurred during catheter placement was observed for 5 days after the event and did not reveal any neurological signs or symptoms.

Haemodynamic changes

Overall, haemodynamic changes observed during Studies I–V did not differ from those otherwise seen during the routine use of continuous neuraxial analgesia. In any case, when pronounced haemodynamic changes occurred they responded well to treatment.

In Study I, eight patients required the rate of their epidural infusion to be halved, in five of them the infusion rate was returned to the initial level when haemodynamics had stabilized. Although this observation showed no difference between the groups, it is important because the plasma concentrations of ropivacaine and fentanyl became affected (see below Discussion).

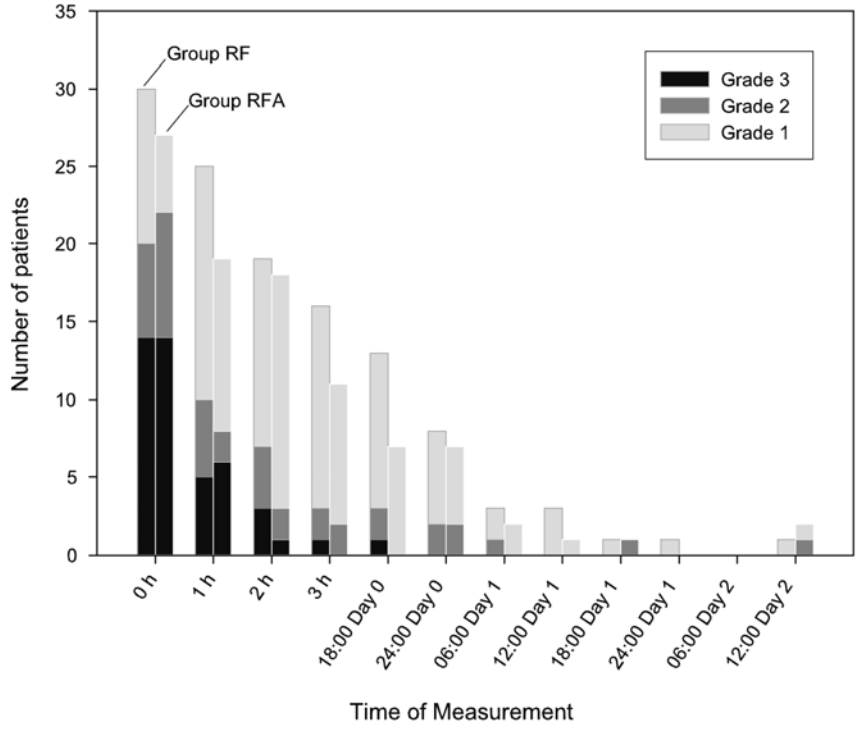
In Study III, mean arterial pressure (MAP) and heart rate measured at the interviews were slightly lower in Group RFC as compared to Group RF (statistically significant for the MAP with a mean difference of 5 mmHg ($p<0.002$, $F=10.5$, RM ANOVA)). Additionally, when taking into account blood pressure values registered apart from those of the predetermined interviews, systolic blood pressure less than 90 mmHg was observed more often in Group RFC than in RF (Table 4 of Study III). Two patients of Group RFC received three doses of ephedrine i.v. (5 to 10 mg) on the ward during CEA compared to none of those in Group RF.

In Study IV, haemodynamic parameters did not differ statistically between Group R and Group RM. When the spinal infusion was reduced during CSPA, it was mainly to manage hypotension and on some occasions due to a pronounced motor block that had ensued (page 397 and Table 3 of Study IV).

Motor weakness

Motor blockade in Studies I–III was rarely encountered and unaffected by the addition of either adrenaline or clonidine. For instance, the steady decrease in motor block during Study II is shown in Figure 9: Deeper degrees of motor blockade were more often noted during the stay in the PACU and grade 3 did not occur after 18:00 on the day of surgery. In Studies II and III, routine physiotherapy was begun in the vast majority of patients in the morning of Day 1. On six occasions (3 patients per group) of Study III, only limited exercises could be made due to a slight motor block, while in one patient of each group physiotherapy was postponed because of the occurrence of prominent leg weakness. The infusion rate during CSPA was diminished to counter the marked motor block in four patients of Group R and in one patient from Group RM (Figure 2 in Study IV).

Figure 9. Motor blockade during epidural infusion in Study II.



RF=Epidural infusion of ropivacaine and fentanyl. RFA=Epidural infusion of ropivacaine, fentanyl, and adrenaline. Motor blockade as evaluated with a modified Bromage scale [Bromage 1965]: Grade 1=Just able to move knees. Grade 2=Able to move feet only. Grade 3=Unable to move feet and knees.

PDPH

No patient, including the two individuals in whom the dura was punctured (Table 22), complained of PDPH. A 70-year old patient of Group RFC in Study III suffered severe headache on Day 1; computer tomography of the head was performed which revealed no pathology. Intravenous diazepam improved her situation. Six patients belonging to Study IV reported mild, though transient, headaches and lower back pain (Table 4 of Study IV).

PONV

The incidence of PONV did not significantly vary between the groups at any of the predetermined interviews in Study III. However, eight patients suffered vomiting (11 single episodes) in Group RFC as compared to one patient of Group RF.

Pruritus

Pruritus was less frequent in Group RFC than in Group RF at one interview with, however, no difference in the consumption of oral hydroxyzine (Table 4 of Study III).

Postoperative confusion

A number of patients experienced postoperative confusion. Two of these of Study I (both Group RF) removed their epidural catheters. Two others belonging to Study II (one from each group) also became confused and were excluded from further analysis. A 76-year old patient of Group RFC became seriously confused in the afternoon and evening of Day 1; *i.e.*, several hours after the study infusion had been turned off. The following day, he was again co-operative without recall of the previous day. In Study IV, several patients showed signs of postoperative confusion of a mild and transient nature that did not lead to exclusion from the study (no inter-group statistical difference).

Technical problems

Technical problems are summarized in Table 22.

Table 22. Technical problems encountered during Studies I–V.

	Study I	*Study II*	*Study III*	*Study IV*	*Study V*
Identification of assumed epidural space by LOR technique and application of catheter	All 50, including one dura tap followed by puncture at different lumbar level	All 70	All 72	NA	All 30, however, one dura punctured while threading catheter
Failed identification of intrathecal space	0	0	0	1	NA
One or 2 / 3 or more punctures needed to identify intrathecal space	NA	NA	NA	37 / 9	NA
Successful application of spinal catheter	NA	NA	NA	46 of 46, however, initial resistance in two with successful threading of catheter after withdrawal of needle by 1–2 mm	NA
Catheter dislodgement	4 (two combined with post-operative confusion)	0	0	0	2 (during ambulation on Day 2)
Leakage at some point of catheter-adapter-infusion line assembly	0	2	1	4 (all related to tightness of seal between catheter and adapter)	0
Catheter-adapter disconnection	1	0	0	0	0
Leakage of epidural infusion fluid from puncture site	1	1	0	NA	0
Catheter kinking	0	0	3 (two solved by rearranging fixation tapes; one led to early drop-out)	2	0
Technical failure of infusion pump	0	0	1 (defect pump replaced)	0	0

Data are number of patients. LOR=Loss-of-resistance. NA=Not applicable or not available. Day 2=Second postoperative day.

Plasma concentrations and ABPI (Study I)

The plasma concentrations of both fentanyl and ropivacaine increased over time (Figure 2 in Study I). The ropivacaine concentration was significantly higher at 6 h in Group RF as compared to Group RFA (p=0.01, t-test). No further difference in ropivacaine concentrations was noted on the first and second postoperative days (p>0.35, t-test). The fentanyl plasma concentrations, however, remained similar in both groups at each study period (p>0.55, t-test).

Complete ABPI data was obtained in 17 patients of each group with no difference occurring between the groups.

Results of Study V

Epidurographies

Table 23 summarizes the positions of the epidural catheter tips as confirmed by epidurography. Figure 2 of Study V shows some characteristic findings of epidurography: a) positive epidurography with the catheter tip epidurally (Figure 2A and 2B); b) catheter dislodgment but with catheter tip still *in situ* (Figure 2C and 2D); c) catheter tip at the level of an intervertebral foramen (Figure 2E); and d) catheter tip outside of spinal canal (Figure 2F).

Table 23. Positions of epidural catheter tips as confirmed by epidurography in Study V.

Subgroup	*No. of patients*	*Initial position ($Epidgr_1$)*	*Position Day 2 ($Epidgr_2$)*
Epid-Epid	22	Epidural	Epidural
Cath-Dis	2	Epidural	Catheter dislodged
Inter-Foram	1	Intervertebral foramen	Epidural
Paravert	4	Paravertebral	NA
Intrathec	1	Intrathecal[a]	NA

$Epidgr_1$=Epidurography on day of surgery before start of continuous epidural analgesia. $Epidgr_2$=Epidurography on the second day after surgery. Day 2=Second postoperative day. NA=Not applicable.

[a]All catheter positions were verified by epidurography except for the patient in whom the catheter tip was found in the subarachnoid space and cerebrospinal fluid appeared. The presence of the latter was confirmed with a glucose reagent strip.

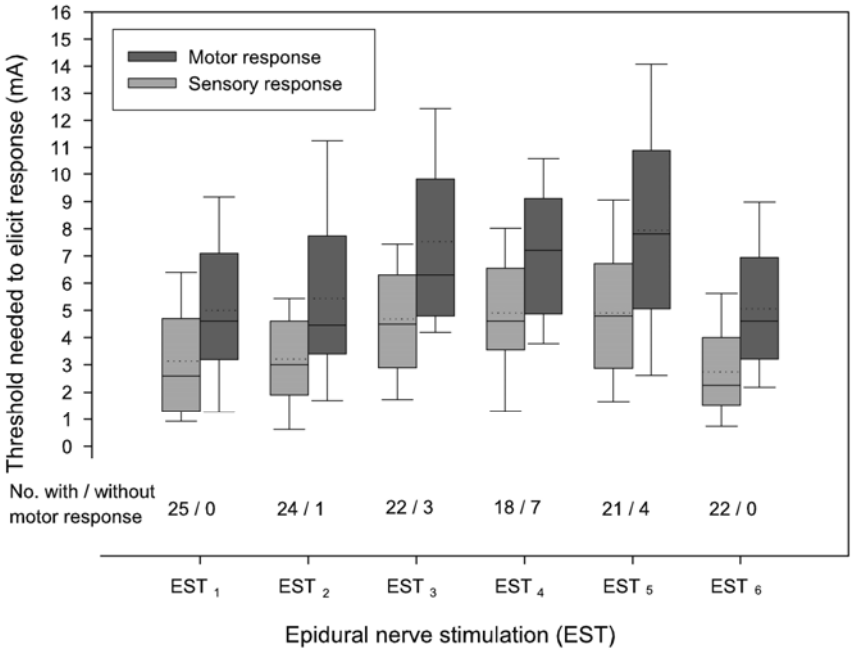
Motor response to EST

In all individuals, EST_1 elicited a motor response: In 28 instances, the *Category* of motor response was in accordance with the spinal column level at which the catheter had been placed; while in the remaining two individuals, the *Category* and the level did not match (nevertheless, they were adjacent). In six patients (all Subgroup *Epid-Epid*), during $EST_{2–6}$, the *Category* of motor response shifted to a neighbouring *Category* as compared to EST_1. At times, the site of the twitching moved within one *Category*, for example, when comparing EST_1 to EST_2.

The current required to stimulate twitching was, on average, higher under the influence of epidurally administered local anaesthetic when compared to EST_1 (Figure 10). Still, several times the EST_2 thresholds were somewhat lower as compared to EST_1 (Table 2 of Study V). The average threshold had virtually returned to EST_1 level when EST_6 was carried out (mean (SD) 128 (40) min after interruption of epidural infusion) (Figure 10). During 107 of 122 measurements with the

catheter tip being located epidurally, EST yielded twitching despite earlier or simultaneous administration of the local anaesthetic ($EST_{2–6}$) (Figure 10).

Figure 10. Threshold current needed to elicit sensory and motor response during EST_{1-6} in Study V.



Only values of measurements where the catheter tip was considered to be in the epidural space based on epidurography. Box plot data are medium (solid line), mean (dotted line), and 25th and 75th percentiles, whiskers are 10th and 90th percentiles. EST was performed at the time points $EST_{1–6}$ (see Figure 1). When calculating box plots, the denominator varied depending on the number of individuals in whom no motor response could be elicited (see numbers at bottom of figure). Changes in motor response thresholds over time were statistically significant. On average, higher currents were needed because of the influence of epidurally administered local anaesthetic ($p<0.0001$, $F=6.5$, RM ANOVA, differences significant regarding $EST_{3–5}$ compared to EST_1 according to Dunnett post hoc test. Missing data, *i.e.*, no threshold values because of absent motor response, were not replaced; therefore, data of only 13 patients were included in this analysis of variance). Data pertaining to sensory response are previously unpublished results (J. Förster *et al.* 2008).

In one patient of Subgroup *Epid-Epid*, EST_1 produced muscle twitching at 10.5 mA; however, $PinPrick_{1-2}$ revealed a distinct bilateral sensory blockade.

In two cases, EST_1 elicited a unilateral motor response at 0.7 mA (Subgroup *Epid-Epid*) and 0.2 mA (Subgroup *Inter-Foram*). When the catheters were pulled out about 1.0 cm, as recommended [Tsui *et al.* 1998], comparable motor responses were attained at 0.7 mA and 1.2 mA, respectively.

In the two patients of Subgroup *Cath-Dis*, where the catheters had slipped out of the epidural space but yet remained *in situ*: EST produced no motor response (maximum output 11.9 mA and 16.0 mA).

In the four patients of Subgroup *Paravert*, motor responses became visible at 7.0, 7.9, 8.2, and 8.9 mA during EST_1. In the latter two patients (threshold >8.0 mA), the grounding electrode was moved to the contralateral thigh, as recommended [Tsui *et al.* 1998]. This manoeuvre, however, did

not affect the site or the strength of muscle twitching. In two patients belonging to Subgroup *Paravert*, when EST was repeated several hours after the last administration of local anaesthetic, one patient demonstrated no twitching (maximum output 14.3 mA), while the second individual showed a muscle response at 5.2 mA.

The patient of Subgroup *Intrathec* showed a bilateral twitching (simultaneous in the right lumbar region as well as the region of the left abdomen). Here, twitching commenced at 0.6 mA and gained in strength at 0.7 mA.

Sensory response to EST

Data in this paragraph are previously unpublished results (J. Förster *et al.* 2008). Average thresholds needed to elicit sensory response are shown in Figure 10. Both the motor and sensory response of EST were usually manifested together within the same area. In some instances, however, the patient stated that they felt the sensation under the grounding electrode. For example, when inspecting the EST_1 reactions of Subgroups *Epid-Epid*, *Cath-Dis*, and *Inter-Foram*, the site of the sensory response was in the same area as that of the motor response in only 15 of 25 patients. In some patients, the neurostimulation test produced sensory sensations in more than one area (Table 24). The location of the sensory response often changed even though that of the motor response remained unaffected during $EST_{2–6}$. Patients with sensory response but without twitching are presented in Table 24.

Table 24. Data concerning sensory response to epidural stimulation test (EST) and technical aspects during EST.

	EST_1	EST_2	EST_3	EST_4	EST_5	EST_6
Sensory response observed at more than one site	7[a]	3[a]	2[a]	2[b]	4[b]	5[b]
Sensory response but no motor response	0	3	6	8	4	2
Need to flush catheter-adapter assembly with sterile 0.9% saline	10	5	2	17	1	9
Need to switch neurostimulator from low to high output mode	6	8	10	14	11	5

Data are previously unpublished results (J. Förster *et al.* 2008). Data are number of patients. The patient with intrathecal catheter tip position is not included.

[a]All patients of Subgroup *Epid-Epid* except one of Subgroup *Paravert*.
[b]All patients of Subgroup *Epid-Epid*. For Subgroup names refer to Table 23.

Sensory blockade after epidural test doses

On two occasions, $PinPrick_2$ remained with no or very ambiguous signs of sensory blockade. In one of these two patients (Subgroup *Paravert*, EST_1 twitching at 7.9 mA), EST_2 and EST_3 failed to evoke any motor response. TD_1 and TD_2 did not produce any detectable sensory block. Epidurography was performed and showed the catheter to be in a paravertebral position. In the second patient (Subgroup *Paravert*, EST_1 twitching at 8.9 mA), EST_2 continued to evoke a motor response at 9.8 mA, but without any response in EST_3. Here, $PinPrick_2$ remained unclear; still GA was induced and surgery performed after which the catheter in the paravertebral position was confirmed by $Epidgr_1$.

Additionally, unilateral blockade at $PinPrick_2$ was noted in two subjects (one Subgroup *Epid-Epid,* one Subgroup *Paravert*). In the patient of Subgroup *Epid-Epid*, $EST_{1–3}$ produced constant twitching at 5.1, 4.2, and 5.3 mA. $PinPrick_2$ revealed a unilateral sensory blockade T5–T11. In the patient of Subgroup *Paravert*, EST_1 gave a muscle response at 8.2 mA, but EST_2 and EST_3 produced no further muscle response. At $PinPrick_2$, the sensory blockade was localized at T11–L3

on the right and possibly at T12 on the left side. In both individuals, it was assumed that the epidural catheters were situated epidurally and so GA was induced.

In still another patient (Subgroup *Paravert*), EST_1 was positive at 7.0 mA, but EST_2 and EST_3 failed to elicit any muscle contraction. However, satisfactory bilateral sensory blockade was found at $PinPrick_{1–2}$ and thus the study was continued.

Technical and other aspects related to EST

The epidural catheter-adapter assembly often needed flushing with physiological saline because of interruption of the electrical circuit (Table 24). During two EST_1 measurements, the output of the neurostimulator oscillated considerably in spite of repeated saline flushing, and in a further instance, when the electrical circuit became disconnected, a slight movement by the patient was sufficient to reinstate the current.

The mean (SD) maximum current delivered in the low output mode was 8.8 (0.9) mA and frequently it became necessary to switch the neurostimulator to the high output mode (Table 24). However, even then the neurostimulator was often incapable of delivering 16 mA.

EST_2 was interrupted on one occasion because the patient experienced paraesthesia in one leg without having any associated visible muscle response. In a second patient, EST_6 caused increasing pain at the site of surgery. The patient reacted with ‘avoiding’ movements of his upper trunk which, in turn, made the determination of the EST threshold unreliable.

Sometimes, the exact determination of the motor response threshold or the disclosure of the motor response as such was influenced by breathing, shivering/tremor, nervous giggling/weeping, and abdominal aorta pulsation.

Discussion

Primary hypothesis

The addition of clonidine to CEA with low-dose ropivacaine and fentanyl somewhat improved postoperative analgesia after TKA when compared to the control group (III). CSPA with low-dose ropivacaine (maximum 1 mg/h) and morphine (maximum 8 µg/h) or ropivacaine (maximum 2 mg/h) offered adequate pain relief after peripheral arterial bypass surgery but without any clinically important difference between the groups, *e.g.*, with regard to the degree of motor blockade (IV). Apart from these results, the primary hypothesis of the present work could not be confirmed, *i.e.*, that the efficacy and quality of continuous neuraxial postoperative analgesia would be improved with the use of the adjuvant drugs and applied technical means (I–V). The addition of adrenaline into a combination of low-dose ropivacaine and fentanyl had no beneficial effect on CEA which was given at a lumbar level following vascular surgery (I) or TKA (II), and finally, EST produced no clear advantage in providing effective CEA in adult patients undergoing major abdominal surgery or thoracotomy (V).

Adrenaline

Ineffectiveness of adrenaline in lumbar epidural analgesia (LEA)

Adrenaline did not aid the efficacy or tolerability of LEA when added in concentrations of 2 and 4 µg/ml to an infusion of low-dose ropivacaine-fentanyl after arterial bypass surgery of the legs (I) and TKA (II), respectively. The patients of the adrenaline Group RFA in Study II with significantly higher amounts of epidurally administered drugs tended to have higher pain scores and higher numbers of breakthrough pain, and needed more doses of rescue medication. The inter-group differences reached statistical significance at two interviews with higher pain scores and less satisfaction in patients of Group RFA (II). However, these differences were of a limited extent and require cautious interpretation. Focusing on the epidural consumption of drugs after two days, the mean difference between the groups was small, 40 ml (95% CI 5–75 ml). In addition, this difference might be, at least in part, explained by the fact that RFA patients less frequently required intraoperative epidural top-ups and their CEA was begun earlier during day as compared to patients of Group RF. On the other hand, these two factors may have occurred by chance and do not explain why the difference in epidurally administered drugs continued to grow over the two study days. Altogether the data in Study II does not permit one to conclude that the adjunct adrenaline had rather antagonistic than additive or synergistic effects with respect to pain relief.

Analgesic effect through α_2-adrenergic receptors in the spinal cord

The lack of improved analgesia by adrenaline in Studies I and II contradicts earlier reports which investigating adrenaline doses of about 10–20 µg/h as an adjuvant to TEA [Baron *et al.* 1996; Niemi and Breivik 1998; Sakaguchi *et al.* 2000; Niemi and Breivik 2002]. However, it does agree with those clinical studies on LEA where adrenaline 0.5 µg/ml [Cohen *et al.* 1998] and 1.0 µg/ml [Cohen *et al.* 1992] offered no major advantage. In these latter studies, adrenaline doses of about 20 µg/h were used as compared to Study I where the average dose of adrenaline was 14 µg/h (range 10–20 µg/h). The negative findings related to adrenaline and LEA have been questioned [Niemi and

Breivik 2003; Niemi 2005] insofar as the adrenaline concentrations used were too low [Cohen *et al.* 1998; Cohen *et al.* 1992] or that the baseline pain intensity and thus the assay sensitivity were also low (Study I) making it difficult to detect any difference between the treatments. However, even with the higher concentration/dosage (4 μg/ml; 12–32 μg/h plus 20 μg as bolus up to two times per hour, if needed) and with considerable baseline pain after TKA, adrenaline had no beneficial effect on LEA in Study II.

Curatolo suggested that a possible explanation for the discrepancy between TEA and LEA could be because of anatomical differences such as the distance between the sites of administration and those of action at the spinal dorsal horn level [Curatolo 2002]. This, in addition to an observation made in volunteers [Curatolo *et al.* 1997] where an adrenaline bolus of 100 μg given epidurally at the lumbar level produced an antinociceptive potential, led to the idea for Study II: that by increasing the dosage of adrenaline added to LEA it might be possible to increase the spinal availability of adrenaline and thus enhance analgesia through an α_2-adrenergic receptor effect. But the results of Study II show that this did not account for the conditions prevailing in the lumbar epidural space. In all probability, many more factors play a part [Curatolo 2002]. These would include the width of epidural space and its amount of fat tissue, the loss of adrenaline due to absorption [Ramanathan *et al.* 1995] and metabolism [Kern *et al.* 1995], altered receptor function in the elderly [Guinard *et al.* 1995], and development of tachyphylaxis to the vasoconstrictive effect of adrenaline [Kihara *et al.* 1999; Miyabe *et al.* 2002].

Vasoconstriction of blood vessels by adrenaline in the lumbar epidural space

It was thought that adrenaline decreases the clearance of epidurally administered drugs by constricting the epidural veins and thus decreasing epidural blood flow [Covino and Wildsmith 1998; Niemi and Breivik 1998]. This would imply that in the presence of adrenaline, the concentrations of epidurally administered drugs would be greater in epidural venous blood. However, measuring from epidural venous blood by a microdialysis technique in pigs, adrenaline had no influence on any plasma pharmacokinetic parameter of epidurally given fentanyl [Bernards *et al.* 2003]. Additionally, Bernards and colleagues stated that perhaps the effect of adrenaline on blood flow might vary from one tissue to another found in the spinal canal, *e.g.*, epidural fat, epidural veins, and dura mater. The effects of adrenaline on blood flow are concentration dependent and it may not achieve sufficient concentrations in the epidural fat to produce vasoconstriction. In fact, adrenaline being hydrophilic might be present in such relatively low concentrations in the epidural fat that it rather causes vasodilation through β_2-adrenergic receptors [Bernards *et al.* 2003; Millet *et al.* 1998].

Limited data is available regarding the types of adrenoreceptors in the vessels of the epidural space (epidural venous plexus and vessels of epidural fat tissue) [Guimaraes and Moura 2001]. It may well be that there is a lack of direct experimental proof on the response of the epidural vascular meshwork to adrenaline.

Furthermore, the total effect of adrenaline on CEA appears more difficult to predict when one takes into account the characteristics of the opioid (*e.g.*, lipophilicity) and the local anaesthetic (*e.g.*, vasoconstrictive properties) used in the epidural infusion. Ropivacaine is a lipophilic drug, though less so than bupivacaine which was used by Niemi and Breivik in their original study on adrenaline and TEA [Niemi and Breivik 1998]. Moreover, ropivacaine may have its own vasoconstrictive capacity, when, for example, administered intradermally [Cederholm *et al.* 1994], epidurally [Dahl *et al.* 1990], or intrathecally [Kristensen *et al.* 1998].

Plasma concentrations of epidurally administered ropivacaine and fentanyl

The protocol of Study I did not take into account plasma samples of patients whose rate of epidural infusion required adjustment and thus were removed from the analysis of plasma drug concentrations. When these individuals were added to the drop-outs for other reasons, the number of patients contributing to plasma concentration data fell considerably (Figure 2 in Study I); caution is therefore necessary when interpreting these measurements.

It seemed that although adrenaline initially produced a slight reduction in the ropivacaine plasma concentration, the effect was no further detected 24 and 48 h after the start of the epidural infusion. The small difference in plasma concentrations at 6 h did not correlate with an improvement in pain relief. A similar temporary effect on local anaesthetic plasma concentrations has been demonstrated in earlier trials where adrenaline, used as an epidural adjuvant, decreased plasma lidocaine concentrations for only one to two hours after the start of epidural lidocaine infusion [Kihara *et al.* 1999; Miyabe *et al.* 2002]. Tachyphylaxis to the vasoconstrictive effect of adrenaline may explain this phenomenon. A further explanation for lower ropivacaine plasma concentrations might be because systemically absorbed adrenaline stimulates cardiac output and thus increases the volume of distribution, hepatic uptake, and renal excretion of ropivacaine [Sharrock *et al.* 1991]. However, the addition of adrenaline to CEA did not effect the systemic blood circulation with respect to the haemodynamic parameters measured in Studies I and II.

Fentanyl plasma concentration was not influenced by the addition of adrenaline which is in accordance with earlier findings [Cohen *et al.* 1992]. This, however, contrasts with results from a TEA study where the delayed systemic absorption of fentanyl was attributed to a vasoconstrictive effect of adrenaline [Niemi and Breivik 1998]. The anatomical differences between the lumbar and thoracic epidural space may contribute to these inconsistent findings.

Summary on adrenaline as an adjuvant to LEA

The results of Study I and II were gathered under strict circumstances and caution must be taken when extrapolating the data to other settings and drug combinations. One, however, can infer that under the conditions of Study I and II the addition of adrenaline to LEA is not recommended.

Clonidine

Effects on efficacy and side-effects of CEA

After TKA in Study III, the addition of the low-dose clonidine to CEA augmented the relief of pain without any signs of clonidine induced haemodynamic instability or sedation. In comparison to earlier studies, the clonidine dosage applied (2 μg/ml, on average 9 μg/h, approximately 220 μg/d) can be taken as a low-dose. Higher doses of clonidine given for postoperative analgesia regularly caused hypotension, bradycardia, and sedation [Mogensen *et al.* 1992; Paech *et al.* 1997; Armand *et al.* 1998].

Several parameters pointed towards an intensification of CEA by clonidine. Group RFC patients, on average, required less epidural drugs as compared to patients from Group RF. Improved pain relief in Group RFC can be deduced as well from the lesser frequency of breakthrough pain episodes at rest. However, the median difference in oxycodone consumption was only 3 mg during 24 h and the lower 95% confidence limit of this difference was zero (95% CI 0–7 mg). In all, there was no major clinical benefit by adding the low-dose clonidine to the CEA mixture of ropivacaine and fentanyl when combined with a multi-modal analgesic regimen including regular paracetamol and rofecoxib.

Unfortunately, the somewhat reduced opioid requirement in Group RFC was not accompanied with fewer side-effects such as PONV. An emetic potential of α_2-adrenergic agonists has been described in animal research and veterinary medicine [Japundzic-Zigon *et al.* 1997]. On the other hand, α_2-adrenergic agonists seem promising allaying PONV in humans [Oddby-Muhrbeck *et al.* 2002; Khasawinah *et al.* 2003].

The present data does not reliably reveal whether pain relief significantly differed between the two TKA studies (II and III). VAS pain scores tended to be higher in Group RFA than in Group RFC, particularly in the early postoperative period (Figure 7 and Figure 8). However, several factors related to the design of the studies forbid a closer comparison – epidural top-ups were given in Study II but not in Study III and the drug concentrations of ropivacaine and particularly fentanyl (3 and 5 μg/ml in Study II and III, respectively) differed.

Despite its limited effect on analgesia, the triple combination used for CEA in Group RFC may have a potential as a second line of treatment when the routine mixture of local anaesthetic and opioid are insufficient to control breakthrough pain or when a multi-modal analgesic regimen is not feasible (*e.g.*, contraindication to NSAIDs).

Choice of 'optimal' drug combination

When planning a trial concerning adjuvant drugs, one aspect is to choose the 'optimal' combination of drugs and their concentrations. Two combinations with presumably similar potency may vary considerably with regard to their side-effect profiles. This difficulty has been addressed in a study regarding TEA [Curatolo *et al.* 2000] (Table 3) and in another with LEA [Sveticic *et al.* 2004] (Table 4). Interestingly, the last combination shown in Table 4 corresponds well to that used in Group RFC (Table 25). The drug combination of Group RFC was not based on the study by Sveticic *et al.* Rather, the dose of clonidine was selected on the premise that it would be, on average, lower than 20 μg/h which was the smallest dose used in previous studies and found to be associated with hypotension [Mogensen *et al.* 1992; Paech *et al.* 1997]. The other components of the CEA regimen in Study III were based upon the routine used in the particular clinic.

Table 25. Comparison of drug mixture used in Group RFC of Study III with results coming from an optimization procedure searching for optimal drug combinations for LEA [Sveticic et al. 2004].

	Group RFC in Study III	*'Combination 4' in [Sveticic et al. 2004]*
Infusion rate (ml/h)	3–7 ml/h	7–15 ml/h
Local anaesthetic concentration	Ropivacaine 2.0 mg/ml	Bupivacaine 0.5 mg/ml
Fentanyl (μg/ml)	5.0 μg/ml	2.4 μg/ml
Clonidine (μg/ml)	2.0 μg/ml	1.0 μg/ml

RFC=Mixture of ropivacaine, fentanyl, and clonidine. LEA=Continuous postoperative epidural analgesia at lumbar level. 'Combination 4'=Refers to Table 4. The two combinations correspond to each other well with a factor of 2 for infusion rate, fentanyl, and clonidine; and a factor of 2 times 2 for the local anaesthetics.

CSA and CSPA

The spinal catheter technique used for CSA and CSPA in Study IV provided good intraoperative haemodynamic control and satisfactory postoperative analgesia. The patients' overall satisfaction with CSPA was good to excellent. The hypothesis, however, that the infusion of low-dose ropivacaine (maximum 1 mg/h) and morphine (maximum 8 μg/h) would result in less motor blockade than ropivacaine alone (maximum 2 mg/h) was not supported.

CSA

The onset of CSA was slow in many instances. One-third of the patients experienced some level of pain at skin incision although the spread of anaesthesia appeared sufficient before the start of surgery as judged by the loss of cold sensation to at least T10. These situations were, however, readily overcome by supportive measures such as small doses of intravenous opioid, neuraxial top-ups, and/or infiltration anaesthesia. The need for such supportive measures should not be considered a failure of the primary regional anaesthesia technique. The evaluation of the spread of CSA is known to be difficult. In a study where small increments of bupivacaine 5 mg/ml were given for CSA and sensory block was assessed by pinprick, a slow onset of the spinal block and the occurrence of pain during incision were noted [Pitkänen *et al.* 1992a]. The adequacy of anaesthesia may be improved by increasing the initial intrathecal dose. Similar problems in assessing the block have been described during CEA with pin-prick and the loss to cold sensation correlating only weakly to the degree of analgesia [Curatolo *et al.* 1999].

In Studies I and IV, the average time for arterial bypass surgery of the lower extremities was approximately 3 h, but often even considerably longer. The use of CSA technique provided a sufficient length of anaesthesia in Study IV. Top-ups were needed to comparable degrees in Study I and IV: 26 of 44 patients receiving intrathecal top-ups after the first hour of CSA (IV) as compared to 26 of 45 patients requiring epidural top-ups (I). In Study IV, three patients moved their legs to such an extent that it interfered with surgery. This particular parameter had not been taken into account during Study I.

As expected, arterial blood pressure and heart rate decreased during the first 60 min of spinal anaesthesia. These changes, however, were minor to moderate with no sudden deterioration in haemodynamic stability. Vasoactive drugs were rarely needed and, if so, in small doses. Whether CSA causes less haemodynamic changes as compared to SSA has been debated with reports in favour [Sutter *et al.* 1989; Morrison *et al.* 1991; Klimscha *et al.* 1993; Favarel-Garrigues *et al.* 1996] and against [Pitkänen *et al.* 1992a; Sabaté *et al.* 1994; Lundorff *et al.* 1999]. Since not all these studies were carried out for peripheral artery graft surgery, they are not directly comparable to Study IV. Some of the inequalities noted between Study IV and other trials [Morrison *et al.* 1991; Sabaté *et al.* 1994; Lundorff *et al.* 1999] might be explained by methodological aspects, as for example, various co-existing diseases [Sabaté *et al.* 1994]; whether invasive CVP control was used or not [Morrison *et al.* 1991; Lundorff *et al.* 1999]; and if the first dose of local anaesthetic was given while the patient was still in the sitting position [Lundorff *et al.* 1999] or only when placed in the supine position after lumbar puncture.

When re-operation for reasons of haemorrhage was needed in the four patients of Study IV, spinal anaesthesia was easy to achieve again by injecting small amounts of local anaesthetic through the catheter. This proved advantageous for both the patient and the anaesthetist, as no further anaesthesia technique was needed.

CSPA

Pain relief was adequate in both groups of Study IV with no clinically significant difference in the amount of oxycodone as rescue medication. Perhaps some patients would have benefited from slightly higher infusion rates with respect to pain relief, but it was decided not to exceed the rate of 0.4 ml/h, as experience with the CSPA technique in vascular surgery patients was limited. The infusion rate was reduced at least on one occasion in nearly half of the patients (20/44). This was done to counteract the moderate hypotension and in some instances for the pronounced motor blockade. However, there were no treatment-resistant periods of hypotension and the infusion rate was re-instated once haemodynamic stabilization was again established.

Ropivacaine was chosen as spinal anaesthetic in Study IV because it is associated with less motor blockade than bupivacaine which was the local anaesthetic used earlier for CSA and CSPA [Van Gessel *et al.* 1995; Standl *et al.* 1995a; Niemi *et al.* 1996; Bachmann *et al.* 1997; Vercauteren *et al.* 1998; Maurer *et al.* 2003; Gurlit *et al.* 2004]. Indeed, the degree of motor blockade was minimal throughout the entire CSPA study period (Figure 2 in Study IV) with three patients of Group R and one of Group RM displaying a motor blockade grade 1 on Day 1. Unfortunately, no conclusion can be reached regarding a possible difference between the Groups R and RM. Yet, the motor blockade appeared to be less marked in this study with ropivacaine as compared to that with bupivacaine [Bachmann *et al.* 1997]. Whereas slightly more than 10% of the patients had a modified Bromage score of 2 after 4 h from the start of CSPA with ropivacaine in Study IV, more than 70% of them manifested a score of 2 or 3 measured 3 h after the start of CSPA with bupivacaine (either bupivacaine 2 mg/h or bupivacaine 1mg/h plus morphine 8 µg/h) [Bachmann *et al.* 1997]. An RCT directly comparing bupivacaine and ropivacaine in CSPA is needed to confirm whether these two local anaesthetics differ as to their analgesic efficacy and their potential to produce motor blockade.

The amounts of ropivacaine given for CSA intraoperatively and the consumption of intrathecally infused drugs during CSPA were somewhat larger in Group RM than in Group R. Although statistically significant, both these differences were, clinically speaking, small and the corresponding lower 95% confidence limits approached zero: The median difference of ropivacaine for CSA was 7.5 (95% CI 0–11.3) mg and the median difference of intrathecally infused drugs during CSPA was 0.4 (95% CI 0.04–0.7) ml. Most likely, both of these differences had little or no influence on pain scores or on the degree of motor blockade in the postoperative period.

The combination of low-dose ropivacaine and morphine was not better than the higher ropivacaine dose alone. In a previous study [Bachmann *et al.* 1997], bupivacaine 1 mg/h combined with morphine 8 µg/h provided satisfactory CSPA, as did bupivacaine 2 mg/h after hip and knee arthroplasty. However, Bachmann *et al.* concluded that the combination was desirable because it produced less motor blockade. The small dose of intrathecal morphine given to patients in Group RM did not lessen the need for oxycodone during the 24 h following CSPA, *i.e.*, there was no carry-over effect of the intrathecal morphine.

No reliable conclusion can be drawn from the data concerning the question as to whether pain scores were higher during CSPA when compared to CEA in Study I (Figure 6) because the two trials were not designed to undergo a direct comparison.

As stated above, CEA may have beneficial effects on graft patency after arterial bypass surgery (Table 2). This outcome parameter was not part of Study I and IV. It remains open as to whether CSPA might provide a similar advantageous consequence on graft performance as does CEA.

EST

EST was often cumbersome to perform and the identification of the motor response threshold next to the interpretation of the test results were several times complicated. Neither did EST help to identify the four patients whose catheters were outside the spinal canal preoperatively. On the other hand, it did correctly detect the single case of intrathecal catheter location. During most of the measurements with an epidurally positioned catheter tip, EST elicited twitching despite the preceding or simultaneous administration of epidural local anaesthetics.

After its original description [Tsui *et al.* 1998], EST has been part of numerous reports [Tsui *et al.* 1999c; Tsui *et al.* 1999b; Tsui *et al.* 1999a; Tsui *et al.* 2000; Goobie *et al.* 2003; Tsui *et al.* 2004a; De Medicis *et al.* 2005; Tsui *et al.* 2007; Charghi *et al.* 2007]. Study V corroborated some of the earlier findings but has also linked EST to several difficulties previously not described.

Catheter tip epidurally or outside of spinal canal

EST_1 produced a motor response in all patients including the four from Subgroup *Paravert*. In the latter, twitching thresholds were slightly below or above 8 mA. It has been suggested that if motor response is seen at a current between 8 and 10 mA, the motor response should change in terms of strength or location when the grounding electrode is relocated [Tsui *et al.* 1998]. This double-check method did not uncover the paravertebral catheter position in the two patients with EST_1 at 8.2 and 8.9 mA. One false negative EST_1 occurred at 10.5 mA; this level of current approaches the 10 mA initially suggested to be the limit for distinguishing between epidural and non-epidural catheter positions [Tsui *et al.* 1998]. Interestingly, Tsui recently stated that currents above 10 mA are quite often needed [Tsui 2006]. However, it remains unclear as to where to place the upper cut-off, at 10 mA [Tsui *et al.* 1998], 11.1 mA [Goobie *et al.* 2003], or even 15 mA [Tsui 2006].

Catheter tip intrathecally or on a nerve root

The lower limit <1 mA is always to be considered as a warning sign for the possible subtotal or subarachnoid catheter position [Tsui *et al.* 1998; Tsui 2006]. This concept [Tsui *et al.* 1998; Tsui *et al.* 1999a; Tsui *et al.* 2004b; Lena and Martin 2005; Tsui *et al.* 2005b] is supported by the findings from the patient with dura tap in Study V where bilateral twitching began at 0.6 mA and grew obviously in strength at 0.7 mA. Indeed, a suspicion of a dura tap was linked with the spontaneous and constant back-flow of a clear fluid through the catheter. However, appearance of cerebrospinal fluid is not a matter of course in such a situation and there are reports of intrathecal drug administration in spite of a negative aspiration test [Tsui *et al.* 1999a].

The original EST description stated that a situation where the catheter is epidurally but directly against a nerve root may result in a motor response <1 mA [Tsui *et al.* 1998]. It has been debated whether such a condition (against-nerve-root-position, unilateral, segmental twitching combined with a negative aspiration test) should be taken as a negative rather than a positive EST test result [Tsui *et al.* 1998; De Medicis *et al.* 2005; Tsui 2006]. Such unilateral, segmental responses at <1 mA were encountered in two patients during EST_1 in Study V.

EST as a monitor of catheter location during CEA

On average, an increase in milliamperage was needed to produce a motor response following the injection of local anaesthetic (Figure 10). This observation is in agreement with previous studies [Tsui *et al.* 1999b] and has been promoted as a possible tool to monitor the clinical effect of repeated epidural local anaesthetic [Tsui *et al.* 1999b]. Whether EST might be a useful measure to ensure the position of the catheter during CEA remains unanswered from Study V. There are, at

least, several observations which give reason to doubt this: a) the lower thresholds in some patients following epidural local anaesthetic; b) the *Category* of motor response or the site of motor response within a *Category* unpredictably changed from one EST to another; c) the false positive EST results; and d) the false negative EST results during CEA on several occasions (no motor response during EST_{2-5}, Figure 10). One possible reason for these observations is that when the patient moves, the soft catheter tip bends within the epidural space and this, in turn, may greatly influence the threshold and the site of response. Yet, when EST_6 was performed some 2 h after the termination of CEA, consisting of a low-dose opioid-local anaesthetic infusion, a positive EST result was observed in all 22 individuals having an epidurally situated catheter (Figure 10). This indicates that EST might be helpful in verifying a possible catheter dislodgment during CEA.

Interpretation of the sensory response

The heterogeneous results from Study V show that questioning the patients for the sensory response to EST only decreases the diagnostic accuracy of EST. This is in contrast to an earlier assertion suggesting that the overall sensitivity of EST might be increased by including subjective sensory responses [De Medicis *et al.* 2005].

EST and quality of CEA

All 25 patients receiving CEA had sufficient pain relief as assessed by PHH-scores, VAS pain scores, and rescue medication requirement over the first two postoperative days. Whether EST contributed to this remains unclear. CEA failures due to initially misplaced catheters would have occurred without epidurography.

Promising EST performance results were found in earlier studies which compared EST with other indirect methods [Tsui *et al.* 1998; De Medicis *et al.* 2005; Charghi *et al.* 2007]. These are difficult to compare to the present results which have been based on a direct confirmation method, *i.e.*, epidurography. For example, evaluating sensory blockade following a local anaesthetic test dose [Tsui *et al.* 1998; De Medicis *et al.* 2005; Charghi *et al.* 2007] includes subjectivity on both the side of the patient and of the investigator. Besides, whereas in Study V the catheter positions were traced systematically from the moment of catheter placement until the second postoperative day, earlier studies only focused on previously placed epidural catheters [Tsui *et al.* 1998; Tsui *et al.* 1999a; Tsui *et al.* 2000] or on the time of catheter placement [Tsui *et al.* 1999b; Goobie *et al.* 2003; Tsui *et al.* 2005a]. Other methodological differences are also apparent. In Study V, the efficacy of CEA was evaluated systematically until Day 2. Other reports on the efficacy of epidural postoperative analgesia, however, were either incomplete [De Medicis *et al.* 2005; Charghi *et al.* 2007], or included data gathered from very young children who would be unable to express in detail the effectiveness of a particular pain treatment regimen [Tsui *et al.* 2001; Tsui *et al.* 2004a]. In some studies, confirmation was attempted with an anteroposterior X-ray but without contrast medium [Tsui *et al.* 2001; Goobie *et al.* 2003; Tsui *et al.* 2004a; Tsui *et al.* 2006; Tsui *et al.* 2007]. Although epidurography is far from being a routine technique, it was used as the reference diagnostic test in Study V.

There is no blinded RCT yet available in which the influence of EST on the efficacy of postoperative epidural analgesia had been investigated. Goobie *et al.* carried out an open trial of 30 paediatric patients who received a thoracic epidural catheter inserted under general anaesthesia. They stated that the addition of EST was of no benefit when used with directly placed epidural catheters [Goobie *et al.* 2003].

Technical and methodological aspects

It remains speculative as to why previous studies did not report difficulties in performing EST such as the frequent need for saline flushing, the influence of respiratory cycle on the often barely visible motor response, and that often the maximum output of the neurostimulator did not reach the implicit 16 mA. Another possibility might be insufficient experience with the EST technique; however, when dealing with an alleged simple method one might expect the learning curve to be steep and short. The investigators were aware of the epidurography results when performing $EST_{4–6}$ in Study V. This is in par with earlier studies in which the researchers were also not blinded to results of the comparator method [Tsui *et al.* 1998; De Medicis *et al.* 2005; Charghi *et al.* 2007]. Finally, the findings of Study V must be interpreted with caution because of the small number of patients studied.

Complications, side-effects, and technical problems

Due to the small patient population investigated, Studies I–V provided only limited data to determine the association between the continuous neuraxial techniques and the postoperative complications and side-effects such as PONV, postoperative confusion, and head- and backache. However, the incidence of PONV, for example, is comparable to the results of meta-analyses [Block *et al.* 2003; Dolin and Cashman 2005]. PONV can be partly attributed to the opioids added to the drug infusions used for CEA and CSPA, as well as to those used as rescue medication [Block *et al.* 2003; Dolin and Cashman 2005]. Results from Study IV confirm that PDPH does not pose a major problem of CSA, particularly in the elderly and in conjunction with CSPA [Denny *et al.* 1987; Mahisekar *et al.* 1991]. Postoperative confusion-delirium may be often encountered in the older patient and following major orthopaedic surgery [Williams-Russo *et al.* 1992; Bekker and Weeks 2003].

The rate of complete CEA failures from the initiation of treatment was about 5% (9/192 Studies I–III, Table 15). In retrospect, when adding to this amount the two patients who were prematurely excluded because of insufficient CEA (see text on page 42), as well as the four patients of Subgroup *Paravert* (Table 23) who were at risk of experiencing an unsuccessful CEA, then the total CEA failure rate would rise to 7% (15/217, Table 16). Unfortunately, in Studies I–III, the number of CEA failures arising from a misplaced catheter was not an investigated parameter. In Study V, four of the 40 catheters were initially located outside the spinal canal. This incidence is similar to that seen in an investigation where the rate of patients with unrecognized incorrect placement of thoracic epidural catheters was 10%–15% [Rigg *et al.* 2002]. Premature epidural catheter dislodgement was observed in almost 3% of CEA treatments (6/217). In earlier trials, this incidence has been somewhat higher, 6%–12% [Scott *et al.* 1995; Dolin *et al.* 2002].

The success-failure ratio of CSA in Study IV is comparable to the results from a large prospective study where failure rates were 1.0% and 1.5% for SSA and CSA, respectively [Puolakka *et al.* 2000a]. The CSPA technique was not free of obstacles, *e.g.*, catheter kinking and leakage at the site of the catheter adapter connection. Nevertheless, these problems were overcome and did not cause any exclusion in the 44 CSPA patients in Study IV.

CEA and CSPA involve interventions and devices and as such are prone to technical problems. Such difficulties were encountered during the studies here to degrees which are comparable to previous reports [Silvanto *et al.* 1992; Pitkänen *et al.* 1992b; Niemi *et al.* 1994; Scott *et al.* 1995; Ready 1999; Puolakka *et al.* 2000b]. These problems include difficulties met when applying prolonged neuraxial analgesia through an indwelling catheter and when using medical mechanical devices. For example, leakage at some point of the catheter-adapter-infusion line, disconnection of

the catheter from the adapter, catheter kinking, premature catheter dislodgement, and infusion pump failure were noted. The technical problems, however, did not lead to any apparent harm in any of the patients.

Limitations of Studies I–V

Only a single-dose of the α_2-adrenergic agonists adrenaline and clonidine was investigated in each of the Studies I–III which can be regarded as a limitation. Had the study protocols included a larger range of drug concentrations the results would have had a wider applicability.

Studies I–IV did not take into account whether CEA and CSPA affected long-term outcome variables such as the quality of recovery of the operated leg, hospital discharge times, and resumption of normal activities of daily living. For example, it would have increased the value of Study IV to examine whether CSPA would have any preventive effect on the development of neuropathic pain after peripheral vascular surgery [Greiner *et al.* 2004].

Limitations of Study V are debated above under the heading: EST – Technical and methodological aspects.

Future research

Adrenaline

Further basic research is required as concerns the epidural vascular meshwork and its reactivity to adrenoceptor agonists. It would be of utmost interest to measure drug concentrations directly from the epidural space in humans in analogy to the microdialysis technique used in animals [Bernards *et al.* 2003]. Future studies on adrenaline as an adjunct to CEA should take into account the dose-effect relationship and the influence of a bolus administration *versus* a continuous infusion.

Clonidine

Future investigations with clonidine as an adjuvant to local anaesthetics and opioids for CEA should employ various concentrations of clonidine. In that respect, when contemplating study designs with higher complexity in the future the results from investigations such as the optimization procedure studies (see above under the heading: Clonidine – Choice of 'optimal' drug combination) [Curatolo *et al.* 2000; Sveticic *et al.* 2004] should be considered.

Triple combinations of clonidine, local anaesthetic, and opioid have been studied also in conjunction with intrathecal pain management [Grace *et al.* 1995; Paech *et al.* 2002; Sites *et al.* 2003]. In these studies, clonidine was given in boluses of up to 75 µg. Although such single-dose methods do not require spinal or epidural catheters, they do bear the risk of significant hypotension [Grace *et al.* 1995; Paech *et al.* 2002; Sites *et al.* 2003]. Therefore, it might be of interest to study the administration of a low-dose combination of clonidine, opioid, and local anaesthetic using the CSPA technique.

CSA/CSPA *versus* SSA/CEA

An RCT comparing the CSA/CSPA technique with the SSA/CEA method given for peripheral arterial bypass surgery seems warranted. Such a study could address several of the questions raised in Studies I and IV: a) the intraoperative haemodynamic stability particularly in the early phase of anaesthesia; b) the degree of intraoperative motor blockade and its influence on surgical conditions specially in the later phase of the operation, *i.e.*, during anastomosis of the vessels; c) the efficacy

and tolerance of postoperative analgesia and its possible effects on outcome, *e.g.*, mobilization, graft patency, and development of chronic pain.

EST

While EST could not increase the confidence of providing effective CEA in Study V, the results do not allow the abolishment of the EST technique together with many of its potential benefits mentioned in the literature. Only recently, after the completion of Study V, a new catheter set (StimuLong Tsui Method®, Pajunk GmbH, Geisingen, Germany) for plexus and epidural anaesthesia was marketed. Due to certain properties this catheter may facilitate to perform EST without an additional adapter (Johans ECG adapter®, Study V) and without the need to flush the catheter. Thus, it might improve the feasibility and reliability of the test. Future EST studies should address such equipment-related issues in addition to the study design considerations mentioned earlier in this discussion (randomized, controlled, blinded trial; EST both at the time of catheter placement and repeatedly during CEA).

Conclusions

1. Adrenaline, in concentrations of 2 μg/ml and 4 μg/ml, failed to contribute to the efficacy or tolerability of lumbar continuous epidural analgesia when added to low-dose infusion of ropivacaine and fentanyl after arterial bypass leg surgery and following total knee arthroplasty, respectively. Thus, the use of adrenaline as an adjuvant to lumbar continuous epidural analgesia cannot be recommended under the circumstances of Studies I and II.
2. The adjuvant clonidine provided only slightly enhanced pain relief of lumbar continuous epidural analgesia when infused in doses of 6–14 μg/h together with a low-dose ropivacaine-fentanyl mixture after total knee replacement. In these low doses, clonidine had no beneficial, but also no marked detrimental consequences on the side-effect profile of the pain treatment regimen. Hence, the triple combination with clonidine may be considered as a second line treatment.
3. The continuous spinal anaesthesia technique utilizing a 28G microcatheter proved useful for arterial bypass surgery of the lower extremities. The main advantages were stable intraoperative haemodynamic control, ease of topping-up during prolonged surgery, as well as the ease of providing for spinal anaesthesia when revision surgery became necessary. Continuous spinal postoperative analgesia through the spinal catheter, already in place, provided adequate pain relief. Nevertheless, these results should be corroborated and directly compared to the combination of single-dose spinal anaesthesia and continuous epidural analgesia.
4. The epidural stimulation test, which has been earlier introduced as a simple and reliable method to verify the epidural catheter position, was found here to be more difficult to perform than expected and was associated with problems of interpretation. It was not helpful for the accurate determination of the epidural catheter position at the moment of its placement nor when applied repeatedly during the course of continuous epidural analgesia. The possible role of the epidural stimulation test in quality assurance of continuous epidural analgesia remains to be established.
5. The incidences and types of technical problems during continuous epidural and spinal anaesthesia and analgesia encountered in Studies I–V are comparable to those of earlier reports. Unrecognized erroneous placement of epidural catheters and changes of the catheter tip position to less favourable sites (*e.g.*, slipping out of the epidural space but still remaining *in situ*) during continuous epidural analgesia are everyday challenges in the clinical arena. An easy-to-use and reliable test for the identification of such situations remains to be developed.

Acknowledgements

The present work was carried out in the Meilahti Hospital (Studies I, IV, and V) and the Surgical Hospital (Study III), both part of the Helsinki University Hospital, Helsinki, Finland; as well as in the Orton Orthopedic Hospital (Study II), Invalid Foundation, Helsinki, Finland.

I express my deepest gratitude and respect:

To Professor Per Rosenberg, my supervisor, for the advice and encouragement given during the past years. He introduced me to scientific work and to the exciting world of regional anaesthesia in the first place. While guiding firmly he was always accessible as an experienced supervisor and passionate researcher. I also appreciate his resolute persuasion to develop constantly the education of residents in anaesthesiology and to propagate on all levels the importance of continuous medical education.

To Docent Timo Salomäki and Docent Pekka Tarkkila, the official pre-examiners of this thesis, for their very constructive reviews of the manuscript.

To my co-authors, Drs. Saana Ikonen, Hilkka Lumme, Vilja Palkama, Docents Ulla Aromaa, Tomi Niemi, Mikko Pitkänen, Timo Seppälä, and Professors Pertti Nevalainen and Markku Salmenperä, for the inspiring and pleasant collaboration. To mention some examples, Timo and Pertti provided the measurements of plasma drug concentrations in Study I, and Saana evaluated with her expertise in neuroradiology all epidurographies of Study V. Special thanks go to Tomi who was a stronghold to me throughout the years. With his calm manner and his solid knowledge and skills, he was like the rock in the often stormy sea of daily clinical and research work.

To Drs. Ilona Ilukka, Edward Munsterhjelm, Mauri Murola, Eija Nilsson, Docents Leila Niemi-Murola and Reino Pöyhiä, Professors Eija Kalso and Kari Korttila, as well as all my colleagues not mentioned though not forgotten, for helping me during the project in a variety of ways.

To the directors of the clinics where the work was carried out for providing me with the facilities; and to the decision makers at the Department of Anaesthesiology and Intensive Care Medicine, University of Helsinki, and the Department of Anesthesia, Orton Orthopedic Hospital, Invalid Foundation, Helsinki, for always kindly arranging my numerous periods of research activity into the busy schedules of clinical work: Docents Ulla Aromaa, Irma Jousela, Olli Kirvelä, Anna-Maria Koivusalo, Mikko Pitkänen, and Tarja Randell, and Professors Leena Lindgren, Klaus Olkkola, Markku Salmenperä, and Seppo Seitsalo.

To the nursing staff of the clinics involved, including the Radiology Department of the Meilahti Hospital (Study V), for their understanding and superb co-operation, and for their warm and skilful patient care. Here, I wish to also mention the Acute Pain Service Nurses Kaarina Onkinen, Aila Tornivuori, Birthe Rhen, and Outi Viitanen, and the Study Nurses Nina Munsterhjelm and Jessica Luukkonen, who all assisted in the follow-up of study patients.

To Docent Dimitri Cozanitis, who so thoroughly revised the text.

To Jari Simonen, for finishing the layout and for preparing the ready-to-print version of the present book.

To my parents, Friederike and Hansgeorg Förster, for their steady loving encouragement. To them belongs the credit for virtually most of my communication skills and fundamental scientific thinking which were necessary to endure during the project. My sisters, Cornelia and Katharina, and their families, for listening to my reports concerning the development of the study projects and for cheering me up many times. Although I could not see my parents and siblings as often as I wished because of the geography, still they were of great support to me.

To my mother-in-law, Kaarina Viherluoto, for the countless hours in which she attended and supported the daily life of my family and, this way, enabled me to concentrate on my work and to participate in scientific lectures and congresses. And to my sister-in-law and brother-in-law, Maiju and Teemu Lehtiniemi, for their interest and support, *e.g.*, with regard to many discussions about biostatistics.

To my cousins-in-law Katri, Hanna, Mikael, Petri and Barbara, for being an important part of my social network.

To all my FiMSIC-friends (Finnish Medical Students International Committee), for being merry and amusing fellows.

To my friends Henna and Leo, Sari and Peik, Satu and Pauli, Martin, and Anke and Nuutti, for their pleasant company.

To my wife Johanna, for her immense patience and continual support and caring throughout this study. And to my children Rasmus, Nanna, and Niklas, who are my pride and joy and who brightened my days. Und nicht vergessen: Wir ernten, was wir säen, säen!

The work was supported by grants from the Helsinki University Central Hospital, the Orton Research Institute, Invalid Foundation, and the Special Governmental Subsidy for Health Sciences Research (EVO), Finland. It was also supported by an unrestricted grant of the Finnish Medical Foundation (Duodecim). These contributions are gratefully acknowledged.

Helsinki, January 2008

Johannes Förster

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Original Publications

Errata

Table 1 of Study I, page 1108, gives incorrect data for type of bypass were presented. The correct figures are presented here, in Table 18, page 46.

On page 398 of Study IV the symbol "≤" was omitted. This should read "Sedation scores were ≤1 in all but one patient, who had a score of 3."