DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
112

DETERMINING THE MINIMUM LOCAL ANAESTHETIC REQUIREMENTS FOR HIP REPLACEMENT SURGERY UNDER SPINAL ANAESTHESIA – A STUDY EMPLOYING A SPINAL CATHETER

ANDRES SELL

TARTU UNIVERSITY
PRESS

Clinic of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Medical Sciences on October 19, 2005 by the Council of the Faculty of Medicine, University of Tartu, Estonia

Opponent: Associate Professor Mikko Pitkänen, M.D, Ph.D., Orton Orthopaedic Hospital, University of Helsinki, Finland

Commencement: November 11, 2005

Publication of this dissertation is granted by the Faculty of Medicine, University of Tartu

ISSN 1024–395X
ISBN 9949–11–171–4 (trükis)
ISBN 9949–11–172–2 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr. 441

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Sell A, Kaasik AE. Spinaalkateetrite kasutamine kliinilises praktikas. Eesti Arst 2003; 82: 839–45

II Käärik E, Sell A. Estimating ED50 using the up-and-down method. COMPSTAT 2004 proceedings, Prague, Springer Verlag, 2004; 1279–85

III Sell A, Olkkola KT, Jalonen J, Aantaa R. The minimum effective local anaesthetic dose of isobaric levobupivacaine and ropivacaine administered via a spinal catheter for hip replacement surgery. Br J Anaesth 2005; 94: 239–42

IV Sell A, Olkkola KT, Jalonen J, Aantaa R. Isobaric bupivacaine via spinal catheter for hip replacement surgery: ED_{50} and ED_{95} dose determination. Acta Anaesthesiol Scand 2005; in press

ABBREVIATIONS

95% CI	95% confidence intervals
ASA	The American Society of Anesthesiologist's Physical Status Grading
CNS	Central nervous system
CSA	Continuous spinal anaesthesia
CSF	Cerebrospinal fluid
CSF velocity	Rate of cerebrospinal fluid motion in cm/s
ED_{50}	Effective local anaesthetic dose in 50% of subjects
ED_{95}	Effective local anaesthetic dose in 95% of subjects
G	Gauge, international calibre unit
GROUP L	Isobaric levobupivacaine group
GROUP R	Isobaric ropivacaine group
L3-4	Lumbar interspace between lumbar vertebra 3 and 4
MAC	Minimum alveolar concentration
MLAC	Minimum local anaesthetic concentration
MLAD	Minimum local anaesthetic dose
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
P	Probability of positive outcome
pKa	Expression of dissociation constant in an equilibrium
PDPH	Postdural puncture headache
SD	Standard deviation
T10, T12	Thoracic dermatome level, 10,12, etc.

1. INTRODUCTION

The speciality of anaesthesia has seen major advances thanks to the development of safer anaesthetic agents and techniques, improved knowledge of pain physiology and pain management, and incorporation of a better understanding of perioperative pathophysiology into perioperative care. The last two to three decades have seen an increase in the use of regional anaesthesia techniques for both anaesthetic and analgesic indications in almost all surgical subspecialties. Primarily this has been the result of an increasing awareness of the benefits that those methods can bring to an aging population receiving many new forms of drug therapy for a wide range of intercurrent disease and undergoing a constantly evolving spread of surgical procedures. The most obvious of those benefits is a reduction of postoperative pain. Recently published outcome data have suggested that patients undergoing regional anaesthesia or regional anaesthesia combined with general anaesthesia may actually have decreased morbidity and mortality when compared with patients undergoing general anaesthesia alone (Rodgers et al., 2000; Rasmussen et al., 2003).

There is increasing evidence that for hip arthroplasty techniques using regional anaesthesia do not only have a pronounced inhibitory effect on the stress response but also have beneficial effects on outcome variable such as blood loss and thromboembolic complications (Modig et al., 1983; Jørgensen et al. 1991; Kehlet, 1994; Kehlet and Wilmore, 2002). The metabolic effects of afferent blockade with local anaesthetics are further enhanced if the block is maintained postoperatively for pain treatment (Kehlet, 1998).

One of the most often used techniques of regional anaesthesia is a spinal anaesthesia. Spinal anaesthesia is an old, simple and safe anaesthetic technique (Bier, 1899; Dripps, 1954). Spinal anaesthesia interrupts transmission of nerve impulses produced by the injection of the local anaesthetic into the subarachnoid space. Single shot and continuous applications are techniques for providing spinal anaesthesia. Continuous spinal anaesthesia (CSA) is the technique of producing and maintaining spinal anaesthesia with small doses of local anaesthetic, which are injected intermittently into the subarachnoid space via an indwelling catheter. A continuous technique with incremental injections of small and safe doses of local anaesthetic or with very low continuous infusion of local anaesthetic through a subarachnoid catheter produces an effective block compared to single shot spinal anaesthesia with greater haemodynamic stability (Klimscha et al., 1993; Favarel-Garrigues et al., 1996). CSA is now a proved effective technique for producing profound intra-operative analgesia and motor blockade (Denny and Selander; 1998). The use of catheter technique also allows providing flexible pain therapy in the post-operative period (Standl et al., 1995a). Among the development of modern

catheter techniques for spinal anaesthesia in major orthopaedic and vascular surgery recently new local anaesthetics e.g. levobupivacaine and ropivacaine have been introduced into clinical practice. Preliminary results have shown that these newer local anaesthetics may be significantly less carditoxic and neurotoxic than bupivacaine (Scott et al., 1989; Knudsen et al., 1997; Huang et al., 1998; Morrison et al., 2000; Malinovsky et al., 2002; Yamashita et al., 2003). However, little is known about the required doses of various local anaesthetics in major orthopaedic surgery when CSA is applied. This series of studies was designed to assess local anaesthetic dose requirements and some factors affecting them in patients undergoing hip replacement surgery under CSA.

2. REVIEW OF THE LITERATURE

2.1. History of CSA

Spinal anaesthesia was introduced by Bier in 1899 (Bier, 1899). Within seven years after these initial experiences, the concept of CSA was described in 1906 by Dean, a British surgeon, who wrote of placing a needle in the subarachnoid space and leaving it in situ so that repeated doses of local anaesthetic could be injected (Dean, 1906). In 1940, a malleable needle, which could be left in the subarachnoid space allowing intermittent injection of local anaesthetic via a rubber tube, was described (Lemmon, 1940). The catheter technique was first described in 1944 by Edward Tuohy who devised a technique of inserting a ureteral catheter 4–5 cm into the subarachnoid space via a 15-gauge Huber point needle and initiating spinal anaesthesia with incremental doses of local anaesthetic (Tuohy, 1944). He described CSA as a safe and versatile technique without significant problems of postdural puncture headache (PDPH) (Tuohy, 1945). In the early 1950s, a high incidence of paraesthesia and low success rates with CSA was reported, and this led to a decline in the use of this technique (Dripps, 1950). Fears that CSA would result in a higher incidence of PDPH and neurological complications, together with the development of the continuous epidural anaesthetic technique, further discouraged the use of CSA (Curbello, 1949). In 1964, the use of 20- or 21-gauge needles with smaller catheters was advocated (Bizzari, 1964).

When CSA was reintroduced in the mid 1980s, the advantages described were: excellent control of segmental spread and duration; effectiveness of small doses of local anaesthetic; and decreased risk of cardiovascular side effects. The incidence of PDPH also seemed low, especially in elderly patients (Denny et al., 1987). Later microcatheters, which make the CSA technique suitable for use in young patients without incurring an unacceptable risk of PDPH, were popularized (Hurley and Lambert, 1987). However, not only was it difficult to show a decreased frequency of PDPH, but also serious neurological adverse events were reported after the use of microcatheters with high concentration of hyperbaric local anaesthetics (Rigler et al., 1991; Schell et al., 1991). As a consequence, in 1992 the Food and Drug Administration (FDA) of the USA banned the use of spinal catheters thinner than 24-gauge (FDA Safety alert, 1992).

2.2. Nervous system anatomy

The spinal cord is approximately 45 cm long in the adult. It has an elongated cylindrical shape but is somewhat flattened antero-posteriorly. The cylinder is not uniform in diameter, but bears cervical and lumbar enlargements that correspond to the origins of the brachial and lumbo-sacral plexuses. It begins at the level of foramen magnum and below, the spinal cord narrows into the conus medullaris, from which the filum terminale continues down to become attached to the coccyx.

The nerves below the conus medullaris form the cauda equina. The spinal cord has three covering meninges: the dura mater, arachnoid mater and pia mater (see Figure 1).

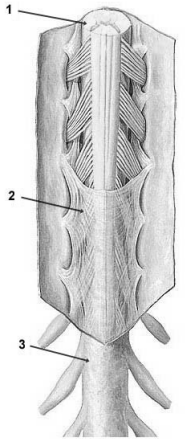

Figure 1. The spinal cord with meninges.
1) The spinal cord
2) The arachnoid mater
3) The dura mater

Dura mater, the outermost membrane, is a tough, fibroelastic tube the fibers of which run longitudinally. Arachnoid mater is the middle of three coverings of the brain and spinal cord. It is delicate nonvascular membrane closely attached to the dura and, with it, ends at the lower border of S2. Pia mater is a delicate, highly vascular membrane closely surrounding the spinal cord and brain. The subarachnoid, subdural and epidural spaces are three compartments which are related to spinal meninges. The subarachnoid space contains the cerebrospinal fluid (CSF). This space communicates with the tissue spaces around the vessel in the pia mater. The subdural space is a potential one only; the arachnoid is in close contact with the dural sheath and is separated from it by a thin film of

serous fluid. The epidural space is the area outside the dura but within the vertebral canal. In extensive areas, the epidural space is empty, and constitutes a plane of contact between the dura with the pedicles and lamina of the vertebra and the ligamenta flava. Elsewhere it contains fat, nerve roots, blood vessels and lymphatics. The epidural contents are not uniformly distributed, but appear in compartments. At birth, spinal cord ends at the level of L3 but rises during growth to end in adult life at the lower border of L1. There are normally 31 pairs of symmetrically arranged spinal nerves, which are attached to the spinal cord by two roots. Both the anterior and posterior roots arise from the cord as several filaments, or rootlets. Each nerve is formed by the fusion of an anterior (ventral) and posterior (dorsal) root (see Figure 2).

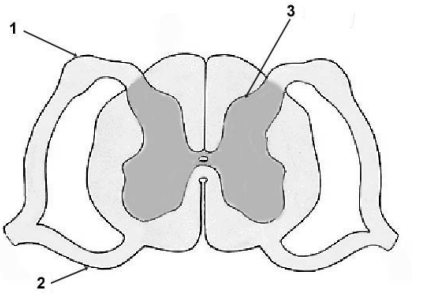

Figure 2. Axial view of spinal cord.
1) Posterior root
2) Anterior root
3) Spinal grey column

The anterior roots are motor and emerge in series from the anterior grey column of the spinal cord. The posterior roots are sensory and enter the cord in series along a postero-lateral groove overlying the posterior grey column. Each posterior root carries a ganglion, immediately distal to which the anterior and posterior roots meet to form a spinal nerve.

The spinal cord is supplied with blood from the spinal branches of the vertebral, deep cervical, intercostals and lumbar arteries. Those spinal branches divide into anterior and posterior radicular arteries which travel along the nerve roots to reach the cord, and divide to form a plexus of arteries in the pia mater. Although the major purpose of the branches is to serve as blood supply to the spinal nerve roots, only a few feed into the anterior spinal artery. There is also a direct supply from the aorta usually at the level of 11th thoracic intervertebral space. This artery is termed the artery of Adamkiewicz and may be a major source of blood to the lower half of the spinal cord in some patients. The

anterior spinal artery supplies the whole of the cord in front of the posterior grey columns. The posterior spinal arteries supply the posterior grey and white columns on either side. There are no arterial anastomoses within the cord, though there is some overlap in distribution. The venous drainage comprises a plexus of anterior and posterior spinal veins that drain along the nerve roots through the intervertebral foramina into the segmental veins. At the foramen magnum the segmental veins communicate with the medullary veins. (Bridenbaugh et al., 1998; Hogan, 1999; Ellis et al., 2004).

2.3. Characteristics of the CSF

Cerebrospinal fluid is formed by secretory cells of the chorioid plexus which project into the lateral, third and fourth ventricles. CSF then flows via the third ventricle through the aqueduct and fourth ventricle to escape by two lateral foramina of Luschka and the median foramen of Magendie into the subarachnoid space around the brain and spinal cord (see Figure 3).

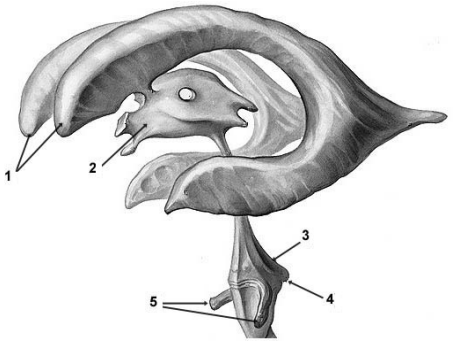

Figure 3. Ventricles of CNS.
1) The lateral ventricle
2) The third ventricle
3) The fourth ventricle
4) Foramen Magendi
5) Foramen Luschka

The total CSF volume in an average adult is about 150 ml, approximately half of which is intracranial. The remainder lies within the spinal subarachnoid space and represents the volume through which the injected solution can distribute. In adults, CSF is produced at a rate of 0.35–0.40 ml min^{-1} or 500–600 ml per day. The turnover time for total CSF volume is about 5–7 hours (Hammock and Milhorat, 1983). Resorption of CSF is mainly into the venous

system via arachnoid villi, which are areas where the arachnoid invaginates into large venous sinuses. Some CSF is absorbed around spinal nerves into spinal veins and through the ependymal lining of the ventricles. CSF is an isotonic, aqueous medium with a constitution similar to interstitial fluid. The mean density of CSF at 37°C is 1.0003 g litre^{-1}, with a range of 1.0000–1.0006 (± 2SD) g litre^{-1}. All the physiological variation is within the fourth place of decimals. Human CSF density is not uniform, however, and varies according to age, sex, pregnancy, and illness (Davis and King, 1954; Döbler and Nolte, 1990; Richardson et al., 1996; Lui et al., 1998; Schiffer et al., 1999; Schiffer et al., 2002).

The volume of the cerebrospinal fluid has obvious relevance as a determinant of dilution of drugs in the subarachnoid space. It has been shown in the measurements of lumbosacral CSF volume that there is great inter-individual variability in CSF volume. From the T11/T12 disc to the sacral terminus of the dural sac, measured by MRI the mean volume for all subjects was 49.9 ± 12.1 ml, with a range 28.0–81.1 ml. This volume was significantly less in relatively obese subjects (42.9 ± 9.5 ml) than in non-obese subjects (53.5 ± 12.9 ml). Abdominal compression decreased CSF volume by 3.6 ± 3.2 ml by displacing tissue into vertebral canal through the intervertebral foramina rather than by changing the venous volume (Hogan et al., 1996). In another study, lumbosacral CSF volumes ranged from 42.7 to 81.1 ml calculated from MRI and those volumes of CSF correlated with pinprick assessments of peak sensory block height and duration of surgical anaesthesia (Carpenter et al., 1998). The lower the CSF volume is, the higher the peak sensory height will be during spinal anaesthesia. It was concluded that the variability in lumbosacral CSF volume is the most important factor identified that contributes to the variability in the spread of spinal sensory anaesthesia (Carpenter et al., 1998). Those findings may explain the unpredictability of spinal anaesthesia in clinical practice (Lacassie et al., 2005). However, these findings will probably not be helpful for guiding local anaesthetic dosing because CSF volume can not be measured before anaesthesia, is highly variable, and is not easily predicted by patient characteristics (Carpenter et al., 1998).

MRI studies have shown that CSF is not static but vigorously oscillates with arterial pulsations (Enzmann and Pelc, 1991; Greitz et al., 1993; Henry-Feugeas et al., 2000). Recently it has been indicated that CSF velocity influences the extent and duration of plain bupivacaine spinal anaesthesia (Higuchi et al., 2004).

2.4. Characteristics of local anaesthetics

2.4.1. Mechanism of action

A propagated nerve impulse involves a wave of depolarisation, followed by repolarisation, passing along the nerve fibre. In the resting mode, the nerve fibres are polarised. The electrical spike caused by depolarisation triggers the adjacent membrane, such that the sodium channels in that section of the fibre open in their turn, allowing the inward flow of sodium ions and depolarisation. Thus each depolarisation/repolarisation that occurs triggers a similar process in the adjacent membrane and this passes along the nerve from one end to other. Local anaesthetic solutions cause reversible blockade of impulse propagation along nerve fibres by preventing the inward movement the sodium ions through the cell membrane of the fibres. This inhibition occurs in a manner that is both time dependent and voltage dependent and results in an increased threshold for activating the action potential, resulting the spread of the electric impulse along the nerve fibres with complete block of their function (Berde and Strichartz, 2000).

2.4.2. Anaesthetic potency, speed of onset and duration of action

The clinically important properties of the local anaesthetics are potency, speed of onset and duration of action. These are determined by the dissociation constant pKa, lipid solubility and degree of binding to protein. Bupivacaine, levobupivacaine and ropivacaine are local anaesthetics of the amino amide group, which have rapid onset and long-lasting action. They have very similar characteristics of chemical and physical properties. A low pKa favours rapid onset of local anaesthetics. The duration of action of those three local anaesthetics is related to high degree of protein binding. The only difference is that ropivacaine is much less lipophylic than the two other molecules. Bupivacaine is a racemic mixture including both S (–) and R (+) enantiomer, while levobupivacaine is the S (–) enantiomer of bupivacaine. Ropivacaine is a pure S (–) enantiomer. Ropivacaine is slightly less potent than bupivacaine (Polley et al., 1999). Studies comparing bupivacaine and levobupivacaine have concluded that the racemate and its active S (–) enantiomer have similar anaesthetic potency (Lyons et al., 1998; Alley et al., 2002). Levobupivacaine has some inherent vasoconstrictor properties, causing longer duration of action compared with bupivacaine in epidural anaesthesia (Kopacz et al., 2000).

2.4.3. Toxicity of local anaesthetics

Local anaesthetics show adverse effects both on the CNS and cardiovascular system if administered in high enough doses. The CNS is usually more sensitive to local anaesthetic toxicity than the cardiovascular system. Thus signs of CNS toxicity are usually evident before signs of cardiovascular toxicity. Spinal anaesthesia does not require large doses of a local anaesthetic, and the risk for systemic toxicity associated with the use of spinal local anaesthetics is not an issue. Based on animal and volunteer studies, both ropivacaine and levobupivacaine are consistently associated with a reduced potential for CNS and cardiovascular toxicity than bupivacaine (Scott et al., 1989; Knudsen et al., 1997; Huang et al., 1998; Morrison et al., 2000; Malinovsky et al., 2002; Yamashita et al., 2003). The short acting local anaesthetic lidocaine was observed to be associated with cauda equine syndrome when used for CSA (Rigler et al., 1991; Schell et al., 1991). Indeed, both experimental evidence and clinical reports show that particularly lidocaine has local neurotoxic effect when applied in high local concentrations (Ready et al., 1985; Rigler et al., 1991; Schell et al., 1991; Malinovsky et al., 2002; Yamashita et al., 2003). Neurotoxicity after spinal injection of lidocaine is the greatest among bupivacaine, levobupivacaine and ropivacaine, and the least neurotoxic potential has been shown with ropivacaine (Malinovsky et al., 2002; Yamashita et al., 2003).

2.4.4. Baricity of local anaesthetics

Local anaesthetic solutions used for spinal anaesthesia are characterized according to their baricity (hypobaric, isobaric or hyperbaric). The baricity of local anaesthetic solution is defined as the density of that solution relative to the density of CSF. The density of local anaesthetic is the mass of the substance relative to its volume. Solutions with baricity of less than 0.9990 are termed hypobaric and solutions with a baricity of more than 1.0015 are termed hyperbaric; solutions with baricity between 0.9990 and 1.0015 are isobaric (Greene, 1985). If sterile water is added to the local anaesthetic solution truly hypobaric solutions will be produced. Hypobaric intrathecal solutions have been defined as those with densities less than three standard deviations below mean human CSF density (Greene, 1985; Davis and King, 1954). If glucose is added the result will be a hyperbaric solution. The temperature of the CSF is the same as body core temperature (between 37°C and 38°C), whereas most spinal anaesthetic solutions are administered at operating room temperature (20–24°C). Local anaesthetics and CSF exhibit a curvilinear decrease in density with increasing temperature. If solutions are administered at room temperature, they will undergo thermal equilibration to body temperature after injection. There will be some local decrease in CSF temperature immediately after

injection, but the temperature of CSF is restored within 2 minutes (Davis and King, 1952; Ernst, 1968).

2.5. Factors affecting the spread of spinal anaesthesia

Many factors affect the subarachnoid spread of local anaesthetic solutions (Greene, 1985; Hocking and Wildsmith, 2004) (Table 1).

Table 1. Factors that may influence distribution of local anaesthetic solutions in cerebrospinal fluid. Modified from Greene (1985) and Hocking and Wildsmith (2004).

Patient characteristics	Clinical technique	Characteristics of anaesthetic solutions
Age	Patient position	Baricity
Height	Level of injection	Volume/dose/ concentration
Weight	Needle type/alignment	Temperature of injectate
Sex	Direction of injection	Viscosity
Intra-abdominal pressure	Intrathecal catheters	Additives
Spinal anatomy	Fluid currents	
Lumbosacral CSF volume	Epidural injection	
Pregnancy	Speed of injection	

The major determinants affecting subarachnoid spread that may be used to control the level of sensory blockade are the dose, the baricity of the local anaesthetic and the posture of the patient (Greene, 1985; Stienstra and Greene, 1991; Hocking and Wildsmith, 2004). Some factors play only a minor or controversial role.

2.5.1. Characteristics of the injected solutions

2.5.1.1. Dose, volume, and concentration of the local anaesthetic

The dose, volume and the concentration of the local anaesthetic have an inseparable relation. The change in one of the variables causes changes in the others. In a study designed to resolve the dose-volume-concentration issue, it has been shown using plain bupivacaine that dosage, and not volume or concentration determines the level of sensory blockade (Sheskey et al., 1983). Those findings have been confirmed for plain, hypo-and hyperbaric bupi-

vacaine, for hyperbaric tetracaine and hyperbaric lidocaine (McClure et al., 1982; Bengtsson et al., 1984; Mukkada et al., 1986; Blomqvist et al., 1988; Van Zundert and De Wolf, 1988; Nielsen et al., 1989; Burgess et al., 1991; Gaggero et al., 1993; Manica et al., 1993; Ben-David et al., 1996; Van Zundert et al., 1996; Kuusniemi et al., 1999). However, in a study determining the minimum effective anaesthetic concentration of hyperbaric bupivacaine for spinal anaesthesia it was found that the block completeness is influenced by both spinal anaesthetic concentration and the dose (Chan et al., 2000). One study has reported that the volume is an important factor of the spread of isobaric tetracaine (King and Wooten, 1995). This result has not been confirmed by others (Ben David et al., 1996; Van Zundert et al., 1996). The total dose of the local anaesthetic also determines the duration of the block (Wildsmith et al., 1981; Labaille et al., 1992; Schnider et al., 1993; Tarkkila et al., 1997).

2.5.1.2. Baricity

One of the most important physical properties affecting the level of anaesthesia achieved after intrathecal administration of local anaesthetic is its baricity. Commercially available bupivacaine has a baricity of 0.9983–0.9990, which means that it is on the edge of being hypobaric, and is best referred as ‘plain’ (Greene, 1985; Horlocker and Wedel, 1993; Schiffer et al., 2002; Wildsmith, 2005a; Wildsmith, 2005b). Commercially available hyperbaric bupivacaine has been widely used. It has been shown that the higher the CSF density, the higher the maximal level of the block was observed for plain bupivacaine solutions (Schiffer et al., 2002). It is important to note that this isobaric range is arbitrarily chosen and not based on clinical evidence. In the individual patient, isobaric solutions may, depending of the CSF density, behave as hypo- or hyperbaric.

In CSA when equal volumes and doses of local anaesthetic are injected with patients in supine, segmental spread of block is greater and onset faster with hyperbaric than either isobaric or hypobaric solutions (Van Gessel et al., 1991).

2.5.2. Clinical technique

2.5.2.1. Posture

The difference between the densities of the local anaesthetics and CSF has a major effect on intrathecal drug spread. This is the result of the action of gravidity. The degree of caudad or cephalad spread will depend on the interaction between density and patient position (Hocking and Wildsmith, 2004;

Korhonen et al., 2005). When using hypo- or hyperbaric solutions, changes in posture once injection has been completed can affect the level of sensory blockade. Recently it has been demonstrated that when the spinal block was performed in the lateral position, baricity had no effect on the spread of the sensory level for bupivacaine, compared to the sitting position, where there was a statistically significant difference in spread with the hypobaric solution producing higher levels of anaesthesia than hyperbaric solution (Hallworth et al., 2005). However, it has been demonstrated that changes in posture even 60 min after the intrathecal injection significantly increases the level of sensory blockade (Povey et al., 1989; Bodily et al., 1992). Using plain bupivacaine, a late posture change resulted in an increase in the level of sensory blockade (Niemi et al., 1993).

2.5.2.2. Level of injection

The level of injection of local anaesthetic into subarachnoid space plays an important role in the distribution of the anaesthetic solutions. Most studies with plain bupivacaine have shown that a higher level of injection results in significantly greater cephalad spread (Tuominen et al., 1989; Taivainen et al., 1990; Sanderson et al., 1994). The results are less consistent with hyperbaric solutions (Sakura et al., 1998). There is wide variation in the configuration of the spinal column, and therefore, accurate identification of the vertebral interspace may be unpredictable. Previous studies have demonstrated inaccuracies in subjects when attempting to identify lumbar interspaces (Hogan, 1993; Van Gessel et al., 1993a; Broadbent et al., 2000). The vertebral interspace selected has been shown 1–4 segments higher then the intended L3–4 interspace in 68% of the cases (Broadbent et al., 2000).

2.5.2.3. Needle type and alignment

The conventional Quincke-type needle has its opening at the end of the needle, causing the injectate to flow out in a straight axial direction. The direction of the bevel of a standard spinal needle has no effect on the distribution of local anaesthetic solutions in CSF (Neigh et al., 1970). The direction of spinal needle lateral-facing openings has been shown to impact block height levels with isobaric local anaesthetics (Urmey et al., 1997). However, it has been demonstrated that a steep paramedian approach of the subarachnoid space with an angle of less than 50 degrees results in more extensive cephalad spread compared with the perpendicular position (Stienstra et al., 1989).

2.5.2.4. Speed of injection

The speed of injection has been investigated extensively, but with conflicting results. Some studies have reported a greater spread with faster injection (Atchison et al., 1989; Janik et al., 1989; Horlocker et al., 1994) while others with slower injection (Stienstra and Van Poorten, 1990; Tuominen et al., 1992) and some studies have shown no difference (Bucx et al., 1993; Van Gessel et al., 1993b; Casati et al., 1998b; Anderson et al., 2001). In general, faster injections produce greater spread with plain solutions, but the effect is less marked with hyperbaric solutions (Hocking and Wildsmith, 2004).

2.5.2.5. Epidural injection

It has been observed that an epidural injection of saline can compress the theca and thus raise the cephalad spread of intrathecal local anaesthetics (Takiguchi et al., 1997). The ability to increase dermatomal spread by epidural volume appears to be time-dependent. Sensory block extension has been significant if epidural saline was injected 5–20 min after bupivacaine spinal anaesthesia (Mardirosoff et al. 1998; Stienstra et al., 1999).

2.5.2.6. Intrathecal catheter position

No correlation was found between the level of the tip of the 20-gauge catheter with three side ports and the achieved sensory level using hypobaric bupivacaine or tetracaine (Van Gessel et al., 1993a). However, it has been shown that caudally directed 28-gauge end-port catheters increased the onset time of analgesia and the dose of isobaric bupivacaine required to achieve a sufficient sensory anaesthesia level (Standl and Beck, 1994). In a study with 19-gauge end port spinal catheters the correlation between the position of the spinal catheter and the spread of sensory blockade of isobaric and hyperbaric bupivacaine was found (Biboulet et al., 1998).

The position of the patient while the catheter is inserted is unlikely to influence the position of the catheter (Standl et al., 1995; Sell et al., 1999). In contrast, in another study patients who had microcatheters inserted in a lateral position and introduced more than 4 cm into subarachnoid space had a higher incidence of being placed caudally compared with for those inserted less than 4 cm (Standl and Beck, 1993).

2.5.3. Patients' characteristics

2.5.3.1. Age, height, weight and sex

There are small increases in cephalad spread of anaesthesia at the advanced age probably due to the age-related changes in spinal anatomy (Cameron et al., 1981; Pitkänen et al., 1984; Racle et al., 1988; Veering et al., 1988). A correlation has been found between body mass index and cephalad spread of analgesia. It is suggested that epidural fat compresses the dural sac, reduces CSF volume and results in the higher spread of anaesthesia in obese patients (Pitkänen, 1987; Taivainen et al., 1990).

The patient's gender has no direct effect on distribution of LA in the subarachnoid space (Greene, 1985). Males tend to have broader shoulder than hips and for that reason the spinal column may have a 'head up' tilt in the lateral position.

2.5.3.2. Spinal anatomy

Scoliosis has no significant effect on the distribution of spinal anaesthetic solutions (Greene, 1985). Reduction of the lumbar lordosis by hip flexion has been shown to flatten the lumbar lordosis which in turn has been revealed to increase cephalad spread (Hirabayashi et al., 2002). In contrast, exaggeration of the lordotic curve has been found to decrease the cephalad spread of hyperbaric solutions in supine position by causing pooling of local anaesthetics in the deepest part of the S-shaped curve (Greene, 1985).

2.5.3.3. Pregnancy

Pregnancy, can affect the spread of spinal anaesthetics (Van Bogaert, 2000). CSF density is lower in pregnant than in non-pregnant women and theoretically, this difference can lead to difference in the spread of local anaesthetic in various patient groups (Richardson and Wissler, 1996).

2.6. Continuous spinal anaesthesia

The use of spinal catheter technique and incremental dosing of local anaesthetic allows the use of small local anaesthetic doses without the risk of failure of the block in normal clinical practice.

2.6.1. Microcatheter (28–32-gauge) technique

The spinal microcatheter was described first by Hurley and Lambert (Hurley and Lambert, 1987). They introduced 32-gauge microcatheters through a fine 26-gauge spinal needle into the subarachnoid space in an effort to reduce the frequency of PDPH associated with CSA. Interest in clinical use of CSA started to grow again. The incidence of PDPH was only 4%, but the technique was associated with many technical problems (Hurley and Lambert, 1990). In subsequent studies, the use of microcatheters was found to be related to more frequent technical difficulties, catheter damage and failure rates when compared to macrocatheters (Silvanto et al., 1992; Pitkänen et al., 1992b; De Andres et al., 1994). The 32-gauge spinal microcatheter was difficult to handle, CSF could not be aspirated and it had a very high internal resistance, making injection of local anaesthetic very slow. In addition, serious neurological complications such as cauda equina syndrome were associated with the use of microcatheter CSA (Rigler et al. 1991; Schell et al., 1991). Increasing incidence of cauda equina syndrome after CSA in the early 1990's prompted the Food and Drug Administration (FDA), the regulatory medicinal agency of the USA to announce a safety alert and in 1992 the FDA banned the use of spinal catheters thinner than 24-gauge (FDA Safety alert, 1992). The mechanism of neurotoxicity induced by local anaesthetics is not clearly understood. With a caudally positioned catheter and the use of hyperbaric, highly concentrated local anaesthetic, such a 5% lidocaine, there is a risk that a poorly diluted local anaesthetic may remain in the caudal part of the dural sac for long enough to cause toxic lesions to nerve roots (Rigler et al., 1991; Schell et al., 1991; Drasner, 1993). However, there is little if any evidence on the mechanisms of neurotoxicity in experimental models (Kanai et al., 2001). The neurotoxicity of local anaesthetics has been demonstrated in vitro by the collapse of growth cones and neurites in cultured neurons (Kasaba et al., 2003).

Thin microcatheters have remained in use in Europe (Petros et al., 1993, Denny and Selander, 1998) and no significant or increased morbidity has been associated with the use of these.

2.6.2. Macrocatheter (18–24-gauge) technique

Tuohy was the first to use an intrathecal catheter, i.e. a No. 4 ureteral catheter inserted through a 15-gauge needle (Tuohy, 1944). After the introduction of microcatheters, the incidence of technical problems and the risk of severe neurological complications have been the major concern over the use of CSA. Presently standard epidural equipment may be used for CSA. In order to improve the technical performance and stability of the catheter, 20–24-gauge catheters are widely used for CSA (Horlocker et al., 1997; Denny and Selander,

1998). Such macrocatheters are expected to be easier to handle and having a lower risk of caudad positioning when compared to microcatheters (Van Gessel et al., 1993a; Denny and Selander, 1998).

Because of a suspected high incidence of PDPH, the macrocatheter technique is today often used only for elderly patients in whom the risk for PDPH is smaller (Mahisekar et al., 1991). In response to the practical limitations of microcatheters and restrictions on their use, the latest development in CSA has been the catheter-over-the-needle system that consists of either a 22-gauge catheter introduced over a 27-gauge spinal needle (Quincke type) or a 24-gauge catheter introduced over a 29-gauge spinal needle, with a tip of the needle protruding a few millimetres outside the catheter. A Crawford-type needle is placed in the epidural space, the 'Spinocath' is then pushed through the dura into the CSF and the needle is pulled out leaving the catheter in the CSF (Spinocath®, BBraun Melsungen, Germany) (Möllmann et al., 1996; Muralidhar et al., 1999) (Figure 4) .

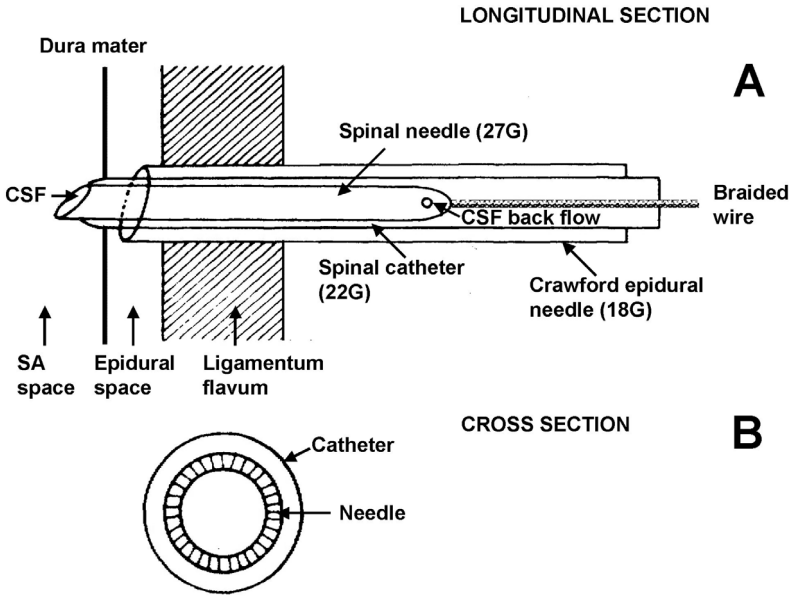

Figure 4. Spinocath, the catheter-over-the-needle system in CSA. Modified from Muralidhar (Muralidhar et al., 1999).

The theoretical advantage of this system is that the hole in the dura has the same size as the catheter, thus minimizing the CSF leak. The macrocatheter size and a tip hole with an additional side hole allows for a high flow rate providing a good mixture and dilution of the anaesthetic agent with CSF by easy barbotage, with consequent reduced risk of cauda equina syndrome (Holst et al.,

1998). After removal of the catheter later in the postoperative period, a local inflammatory swelling of local tissue structures is thought to close the hole in the dura (Yaksh et al., 1986; Denny et al., 1987; Cohen et al., 1994). However, it has been shown that prolonged spinal catheterisation did not reduce the incidence of PDPH (Liu et al., 1993). Compared to microcatheter technique, no major differences regarding technical difficulties or success rate were have been reported (Holst et al., 1998; Muralidhar et al., 1999; De Andres et al., 1999). Scanning electron microscopic examination has been revealed that the Spinocath catheter causes less trauma to the dura mater compared to microcatheters (Holst et al., 1998).

2.6.3. Adverse effects of CSA

2.6.3.1. Haemodynamic effects

One of the reasons to use small initial dosing of intrathecal local anaesthetics is to avoid hypotension. There is some evidence that spinal anaesthesia-induced hypotension increases the risk of myocardial ischaemia which in turn may be avoided using incremental dosing of local anaesthetics through a spinal catheter (Juelsgaard et al., 1998). Clinical studies have shown greater haemodynamic stability with CSA than with single shot spinal anaesthesia or epidural anaesthesia because of the possibility to titrate the level of anaesthesia with small incremental doses of local anaesthetic (Dripps, 1950; Denny et al., 1987; Sutter et al., 1989; Labaille et al., 1992; Klimscha et al., 1993; Robson et al., 1993; Schnider et al., 1993; Collard et al., 1995; Standl et al., 1995a; Favarel-Garrigues et al., 1996; Wilhelm et al., 1997).

2.6.3.2. Postdural puncture headache

The occurrence of PDPH after CSA remains controversial because of wide differences in reported incidences. Some prospective studies have shown a low incidence (Denny et al., 1987; Hurley and Lambert, 1990; Liu et al., 1993; Mazze and Fujinaga, 1993; De Andres et al., 1994; Standl et al., 1995a; Van Gessel et al., 1995; Möllmann et al., 1996), while others found incidences up to 78% (Horlocker et al., 1997; Gosch et al., 2005). The incidence of PDPH in CSA is probably proportionate with the age of the patient, size of the needle used and dural puncture technique (Denny and Selander, 1998; Gosch et al., 2005). The incidence of PDPH following single shot spinal anaesthesia with modern noncutting pencil-point spinal needles has been reported to be 2% and less (Flaatten et al., 2000).

2.7. Spinal anaesthetic agents used for CSA

Racemic bupivacaine is undoubtedly one of the most widely used agents for spinal anaesthesia. There is, however, little data on the minimum dose requirements of local anaesthetics administered intraspinally for orthopaedic, vascular, lower abdominal and or gynecological surgery. The previously reported dose of isobaric levobupivacaine for single shot spinal anaesthesia for hip replacement surgery is 17.5 mg and for isobaric ropivacaine doses 17.5–25 mg have been used (McNamee et al., 2001; McNamee et al., 2002). Levobupivacaine (Chirocaine®, Abbott Laboratories, 2.5 mg/ml) and ropivacaine (Naropin®, Astra Zeneca, 2 mg/ml) have densities of 0.9999 and of 0.9996 mg ml^{-1} at 37°C, respectively. Bupivacaine (Marcaine Spinal®; AstraZeneca AB, Södertälje, Sweden; 5 mg/ml) has a density of 0.9994 mg ml^{-1} at 37°C. These three solutions can be considered isobaric with the cerebrospinal fluid (Lui et al., 1998).

2.8. Determination of the minimum local anaesthetic dose

Because minimum dose requirements are difficult to study minimum local analgesic concentration (MLAC) approach has been created (Columb and Lyons, 1995). MLAC is that local anaesthetic concentration which is effective in 50% of subjects. The MLAC model has been used to evaluate the concentration-response-relationships of local anaesthetic drugs (Columb and Lyons, 1995). This approach allows determination of the median effective concentration (EC_{50}) of local anaesthetic in clinical circumstances using the up-down sequence. The up-and-down sequence was originally introduced to reduce the number of experiments for estimation of a dicotonic variable (Dixon, 1965). Modifications of the MLAC methodology have been employed to study the pharmacodynamics for subarachnoid local anaesthetics and analgesics (D'Angelo et al., 1998; Peng et al., 1998; Arkoosh et al., 1999; Chan et al., 2000; Danelli et al., 2001; Stocks et al., 2001; Saravanan et al., 2003, Frawley et al., 2004; Camorcia et al., 2005; Carvalho et al., 2005). Using somewhat similar study design than MLAC assessment allows estimation of the median effective dose (ED_{50}) of intrathecal local anaesthetics. The ED_{50} is that dose of local anaesthetic which is effective in 50 % of subjects. It can also be defined as the minimum local anaesthetic dose (MLAD) which can be used as a measure of local anaesthetic potency. Still, if single shot spinal anaesthesia is used, even the MLAD concept has its limitations in clinical medicine as it would be inappropriate if only 50% of the patients would be sufficiently anaesthetized. When CSA is used, MLAD can be used to guide in assessing the initial dose, as top-up doses can easily be administered.

2.9. Estimating ED_{50} using the up-and-down method

In some experiments it is not possible to make more than one observation on a given specimen. Once a test has been made the specimen is altered so that the result cannot be obtained from a second test. This situation arises in many fields of research e.g. a response to an incision in clinical medicine is such a sigle test. The technique for obtaining sensitivity data was developed and used in explosive research in 1940's. Because of the specific properties, the procedure is usually called the 'up and down' method and the concept of the up-and-down testing approach was first described by Dixon and Mood (Dixon and Mood, 1948).

The up and down method can be applied to variables that are dicotonic (e.g. either + or –) i.e. a stimulus either causes a response or not. It can be assumed that the probability of a positive response increases monotonically with stimulus level. The rule followed is that if the response at the current stimulus level is positive then the next observation is made at some fixed distance *d* below this level, otherwise it is made at *d* above.

The up-and-down method is suggested for getting data in order to estimate the median of a latent response. An approximate maximum likelihood estimates for the parameters of the (normal) response curve, and approximate formulas have been given for determination of the standard errors of these estimates (Dixon, 1965). It has been pointed out, that using formula of the asymptotic variance, the up-and-down method was 30 to 40 percent more efficient for estimating the median of a latent response than the usual probit analysis method (Dixon, 1965).

2.9.1. Getting data using the up-and-down method

The up-and-down method can be applied to pharmacological assessments e.g. by supposing that the stimulus is a dose. In the up-and-down method the individuals either respond (have positive outcome) or not, depending on the level of the dose. A series of test levels has been chosen with equal spacing *d* between doses. The underlying shape in dose (or log dose) can be assumed normal (Dixon, 1965). The distribution is characterized by two parameters, mean (μ) and standard deviation (σ). The spacing *d* is equal to the initial estimate of σ (Dixon, 1965). A series of trials are carried out following the rule: depending on the outcome for the previous individual, the dose for the next is increased (in the case of negative outcome) or decreased (in the case of positive outcome) by *d* units. Testing continues until the desired sample size has reached. In case of a small sample, the result very much depends on the starting value, which usually requires some prior information (Dixon, 1965). The first test should be performed at the level as near as possible to the expected dose of 50% positive response.

2.9.2. Estimates of ED_{50}

Several formulas for estimating of ED_{50} based on the maximum likelihood approach have been proposed (Dixon, 1965; Brownlee et al., 1953). It has been shown by using up-and-down procedure that maximum likelihood estimators are asymptotically unbiased and have an asymptotic normal distribution (Tsutakawa, 1967).

The estimator for a small sample tests is

$$ED_{50\,1} = X_F + k \cdot d ,$$

where X_F is the final level used in testing and k is obtained from special table based on the maximum likelihood analysis for each possible configuration of responses assuming normal distribution. d is the spacing. The sample sizes for Dixon's k-table vary from 2 to 6 (Dixon, 1965).

The following formula is recommended for sample sizes n>6:

$$ED_{50\,2} = \frac{\sum X_i}{n} + \frac{d}{n}(A + C) ,$$

where the mean of the test level is corrected by a factor, which depends on the constants A and C given in the special table and assigned by test series and numbers of positive and negative response in the final trial (Dixon, 1965).

An alternative estimator has been suggested based only on the peaks and troughs of the response series (Wetherill et al., 1966; Choi, 1971). Then the estimator of ED_{50} based on m modified turning points is:

$$ED_{50\,3} = \sum_{i=2}^{m} \frac{w_i}{m-1} ,$$

where w_i are the m turning points (Wetherill et al., 1966).
Suggested standard error of ED_{50} estimator is approximately equal to

$$\sigma\sqrt{2/n}$$ (Dixon, 1965).

The difficulty of estimation of σ arises from the fact that observations from an up-and-down experiment are not independent. So, the variation within the test is related to the individual variation and a complex method for estimation is necessary.

It is essential that the parameter σ is known within rough limits and assumed that estimates of the median (or the mean) of the response are not sensitive to errors in the guessed value of σ (Brownlee et al., 1953). There are different approaches to estimate standard deviation (Choi, 1971; Williams, 1986). It has been shown on small sample properties of several estimators of ED_{50} that no

estimator seems to have particular advantages compared to others (Kershaw, 1987).

2.9.3. Logistic regression

One of the methods for analyzing the data achieved by the up-and-down procedure is logistic regression or logit analysis. In this method, variable Y^* (latent response) is unobservable continuous random variable such that binary random variable Y takes the value one if and only if Y* exceeds a certain threshold θ. In a clinical trial the latent variable Y* can be considerd as the influence of the dose and Y is the outcome (1/0 – Yes/No). The positive outcome occurs only when the latent response (dose) exceeds the threshold. Thus, the probability P of a positive outcome is P= (Y=1)=P (Y*>θ). This dependence can be written as Y*=α+β Dose+U, where α is slope, β is the regression coefficient and U is the error term. The distribution error can be considered normal. An alternative to the normal error distribution is the logistic distribution that has the advantage of a closed form expression, and the inverse transformation of which is logit. According to logistic distributions, the probability of a positive response P is expressed in following way:

$$P = \left[1 + \exp\{-(\alpha + \beta \cdot Dose)\}\right]^{-1}.$$

Once this relationship is modelled, the ED_{50} can be calculated when the probability P=0.5 which is called inverse prediction. Additional modifications based on logistic model have been proposed (Wetherill et al., 1966; Wu, 1985). In comparison of logistic and normal distribution approaches it has been indicated that the normal distribution provides smaller mean squared error of median response only for very small sample sizes and a relatively bad starting point. For relatively good starting points (close to the median), the logistic distribution provides slightly smaller mean squared error of median response. The up-and-down method allows getting relatively good estimates for median expected dose ED_{50} in the case of small and very small sample sizes (Little, 1974). It is reasonable to prefer the logit model for estimating ED_{50} due to the existence of standard statistical software. The observations in up-and-down experiments can be handled as correlated observations, when the next level depends on the previous result. Such experimental plan reduces the dispersion of observations.

Most estimators of ED_{50} require uniform spacing between stimulus levels. This may be an obstruction to get good estimates, especially when the starting point and estimated σ are not good. Changing the spacing during the experiment using currently the information from the obtained results can be done, but additional simulation studies are then needed (Paul and Fischer, 2001).

3. AIMS OF THE STUDY

The present series of studies was designed to assess the local anaesthetic requirements during CSA in patients undergoing hip replacement surgery. More specifically, the aims were:

1. to review the use of spinal catheter in clinical anaesthesia,
2. to evaluate the used up-and-down method as a technique in estimating ED_{50},
3. to determine the MLAD for isobaric levobupivacaine and ropivacaine in CSA for hip replacement surgery,
4. to determine the ED_{50} and ED_{95} of isobaric bupivacaine in CSA for hip replacement surgery,
5. to assess the effect of catheter tip location on the ED_{50} and ED_{95} of isobaric bupivacaine.

4. PATIENTS AND METHODS

4.1. Subjects

This series of studies includes a review (study I), which was based on observations in two previous studies of 106 patients, published as abstracts, one methodological (statistical) study (II) and two clinical studies (III, IV). The protocols for the clinical studies were approved by the Ethics Committee of Tartu University, and were carried out during the years 2002–2004 in Tartu University Clinics. The written informed consent of all patients was obtained. In total, 99 ASA I–III orthopaedic patients undergoing total hip replacement were investigated (studies III and IV). Common exclusion criteria for CSA were followed in the clinical studies: pregnancy, morbid obesity (body mass index >35 kg m^{-2}), diabetic and other neuropathies, skin infection at the site of injection and other common contraindications for spinal anaesthesia, and allergy to the study drugs.

4.2. Study designs

First paper of the thesis is a review, based on two observational studies by the same author, published previously as congress proceedings. In the first study 75 patients were included where the technique and success were discussed (Sell et al., 1997). In the second study 31 patients were included and this study examined the subarachnoid position of spinal catheters (Sell et al., 1999).

In the statistical study (II), the up-and-down method for estimating ED_{50} for levobupivacaine and ropivacaine was assessed by comparing the theoretical assumptions and acquired results of calculations by Dixon, Wetherill and logit analysis (Dixon and Mood, 1948; Dixon, 1965; Wetherill et al., 1966). The patient data from study III was used in the statistical assessments.

Forty one patients scheduled for hip surgery under CSA were included in study III (Table 2). Using sealed envelopes indicating the study group, the patients were randomly allocated to receive either isobaric levobupivacaine (group L) or isobaric ropivacaine (group R) as the local anaesthetic. Dixon's up-and-down method was used to predetermine the dose of the local anaesthetic for each patient (Dixon, 1965). The success of the block was assessed 20 min after the initial dose of the local anaesthetic. The author performed most of the blocks.

Table 2. Study designs of the clinical studies (III and IV).

Study	Design	N	Drugs used	Assessment of the success of the block	Verification of catheter tip position
III	Clinical Prospective Randomized Double-blind	41	Levobupivacaine 2.5 mg/ml Ropivacaine 2 mg/ml	20 min	NA
IV	Clinical Prospective Randomized Double-blind	48	Bupivacaine 5 mg/ml	20 min	Yes

NA = not applicable

Forty eight patients scheduled for hip surgery under CSA were included in study IV. Using sealed envelopes indicating the study group, the patients were randomly allocated to receive 6, 7, 8, 9, 10 or 12 mg isobaric bupivacaine. Eight patients were allocated to each dose group. The success of the block was assessed 20 min after the initial dose of the local anaesthetic. The author performed all blocks. In study IV, all catheters were injected after surgery with radiopaque dye and examined by radiography for verification of their tip position. The study designs are given in table 2.

4.3. Premedication and monitoring

The patients were not premedicated on the day of surgery. Standard monitoring (including at least electrocardiography, automatic oscillotonometry for blood pressure measurement, pulse oximetry for peripheral arterial oxygen saturation assessment) was used for all of the patients. Clinical end-points for hypotension or bradycardia during anaesthesia and surgery were not defined in the protocol. Nevertheless, the routine practice in the department of anaesthesia in Tartu University Clinics is to define clinically relevant hypotension as a decrease of 20% or more in systolic blood pressure from the baseline values. Similarly, clinically relevant bradycardia is defined as a decrease in heart rate to a level of less than 40 beats per minute. The patients were treated accordingly using ephedrine for both hypotension and bradycardia. After surgery, the patients were monitored in the postanesthesia care unit according to routine procedures of the study site.

4.4. Drugs and equipment

In study III, isobaric levobupivacaine (Chirocaine®; Abbott Laboratories S.P.A., Latina, Italy; 2.5 mg/ml, with a density of 0.9999 mg ml^{-1} at 37°C) and isobaric ropivacaine (Naropin®; AstraZeneca AB, Södertälje; Sweden; 2 mg/ml, with a density of 0.9996 mg ml^{-1} at 37°C) was used. The study drug (3.2 –8.5 ml) was administered manually via the intraspinal catheter with an injection speed of 2 ml in 30 seconds. The dose of the study drug was determined by the up-and-down method of Dixon (Dixon, 1965). Based on the previous clinical experience of the investigators, the intraspinal levobupivacaine dose for the first patient allocated to receive levobupivacaine was 12 mg. Similarly, ropivacaine dose was 14 mg for the first patient in that group. If successful anaesthesia (i.e. sensory and motor block) was achieved within 20 min from study drug injection, the dose of the study drug for the next patient was decreased by 1 mg in that group (levobupivacaine or ropivacaine). Conversely, if successful anaesthesia was not observed, the dose of the study drug for the next patient was increased by 1 mg in that group. If successful clinical anaesthesia was not achieved within 20 minutes, based on the clinical judgment of the attending anaesthetist, additional 2 to 6 mg doses of the study drug were administered for surgical anaesthesia.

In study IV isobaric bupivacaine (Marcaine Spinal®; AstraZeneca AB, Södertälje, Sweden; 5 mg/ml, with a density of 0.9994 mg ml^{-1} at 37°C) was used. Eight patients were randomly allocated to each of the six possible groups to receive 6, 7, 8, 9, 10 or 12 mg isobaric bupivacaine for CSA. The doses were chosen based on the previous clinical experience of the investigators. The volume of 1.2 ml (corresponding to 6 mg) to 2.4 ml (corresponding to 12 mg) of bupivacaine was manually administered via the intraspinal catheter with an injection speed of 1 ml in 15 seconds. Additional doses of 2–8 mg of bupivacaine, based on the clinical judgement of the attending anaesthetist, were administered for surgical anaesthesia via the catheter.

In both studies, a spinal 22-gauge macrocatheter with a tip hole and an additional side hole at 7 mm from tip (Spinocath®; BBraun Melsungen, Germany) (Figure 4) was introduced 2–2,5 cm into the subarachnoid space at L3-4 interspace in the midline with the patient in the lateral position and the side to be operated up.

4.5. Evaluation of the sensory and motor blocks

In both clinical studies (III and IV) assessments of motor and sensory blocks were performed by an anaesthetist who was unaware of the allocated study group. Twenty minutes after study drug administration the following were assessed: (i) response to pinprick at T12 dermatome level on the side of

surgery; (ii) response to transcutaneous tetanic electric stimulation (50 Hz at 60 mA) for five seconds at T12 level on the side of surgery; and (iii) motor function on the side of surgery assessed by modified Bromage scale (0 = no motor block, 1 = inability to rise extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints) (Bromage, 1965). Anaesthesia was considered successful when there was loss of sensation to pinprick and to tetanic electric stimulation, and complete motor block.

4.6. Verification of catheter tip position

In study IV, all catheters were injected after surgery with 0.4 ml of radiopaque dye and examined by radiography for verification of their tip position. Catheter tip location was considered cranial when the tip was over the lower margin of third lumbar vertebra and caudal when the tip was below the lower margin of third lumbar vertebra.

4.7. Statistical analyses

In study II, the methods by Dixon (Dixon, 1965), by Wetherill and coworkers (Wetherill et al., 1966) and logit analysis (Dixon and Mood, 1948) were used for calculation of the ED_{50} and comparison thereafter.

In study III, the sample size was based on previous literature, which has demonstrated that at least six independent pairs of patients with sufficient anaesthesia/insufficient anaesthesia (response/no response-pairs) should provide reliable estimates of MLAD using the up-and-down method of Dixon (Dixon, 1965; Lu et al., 2003). In study IV, the sample size was selected based on previous similar studies (Ginosar et al., 2004).

In study III, Dixon's method was used to calculate the MLAD with 95% confidence intervals. In study IV, the normality of the distribution was first ensured using Kolmogorov-Smirnov test. In addition, the homogeneity of the groups was tested using the analysis of variance. Logistic regression analysis was then applied to estimate the values of ED_{50} and ED_{95} of bupivacaine and to evaluate the possible effect of the catheter tip location to success rate of anaesthesia and bupivacaine dose requirement.

P-values less than 0.05 were considered statistically significant in all the studies.

The data are presented as mean (SD) unless mentioned otherwise.

Analyses were performed with use of statistical package SAS 8.2 for Windows.

5. RESULTS

5.1. Review paper I

In initial own observational studies described in the review, the success rate was 95% and 100% (Sell at.al 1997; Sell at al. 1999). No effect of the positioning of the patient (laying or sitting) was observed on intrathecal direction (cranial-caudal) (Sell et al. 1999)

5.2. Study II

In study II, the different methods estimating the ED_{50} yielded essentially similar results (Table 3).

Table 3. Methods used to calculate ED_{50}

	ED_{50} by Dixon	ED_{50} by Wetherill	ED_{50} by logit analysis
Group L	11.7 mg	11.7 mg	11.4 mg
Group R	12.8 mg	13.0 mg	12.7 mg

5.3. Studies III and IV

The patient characteristics of studies III and IV are presented in Table 4. No differences between the study groups regarding age, weight, height and sex were found. All the patients underwent hip replacement surgery. All spinal catheters were introduced at L3-L4 interspace in the midline with the patient in the lateral recumbent position and the side to be operated up. This position was maintained also during the operation.

Table 4. Patient characteristics. Mean (range) or mean (SD)

Study	Group	No of patients	Age (yr)	Height (cm)	Weight (kg)	Gender (male/ female)
II	Group L	21	66.2 (40–79)	165 (8)	78.2 (11.1)	6/15
	Group R	20	61.6 (37–76)	171 (8)	80.6 (11.7)	10/10
IV	6 mg	8	66.5 (56–75)	168 (8)	84.3 (11.6)	2/6
	7 mg	8	64.0 (54–79)	163 (8)	75.5 (15.6)	1/7
	8 mg	8	65.3 (60–75)	170 (12)	81.6 (22.2)	4/4
	9 mg	8	62.1 (37–73)	164 (12)	76.3 (15.0)	1/7
	10 mg	8	65.1 (44–78)	168 (8)	78.6 (12.2)	5/3
	12 mg	8	67.5 (45–75)	169 (12)	84.3 (11.6)	4/4

5.4. Sensory and motor block

In study III, the sequences of patients with sufficient and insufficient anaesthesia are presented in Figure 5. Anaesthesia was successful by the predetermined criteria in 12 patients in each group after the first bolus dose; out of those patients, the number of patients needing additional local anaesthetic during the entire period of surgery was three in group L and one in group R. The mean (SD) total dose of levobupivacaine required during the entire period of surgery was 15.2 (4.0) mg in the 21 patients of group L and 15.5 mg (3.1) of ropivacaine in the 20 patients of group R.

In study IV, anaesthesia was successful by the predetermined criteria in 32 patients after the first bolus dose. Three out of these patients needed an additional dose of local anaesthetic during the entire period of surgery. Other patients required the top-up dose of local anaesthetic before start of surgery. The mean (SD) total dose of bupivacaine required during the entire period of surgery was 10 (3.6) mg in all 48 patients. The ED_{50} for bupivacaine was 7.1 mg (95% CI 6.0 –8.4) and ED_{95} 12.3 mg (8.9 –15.7) (Figure 6).

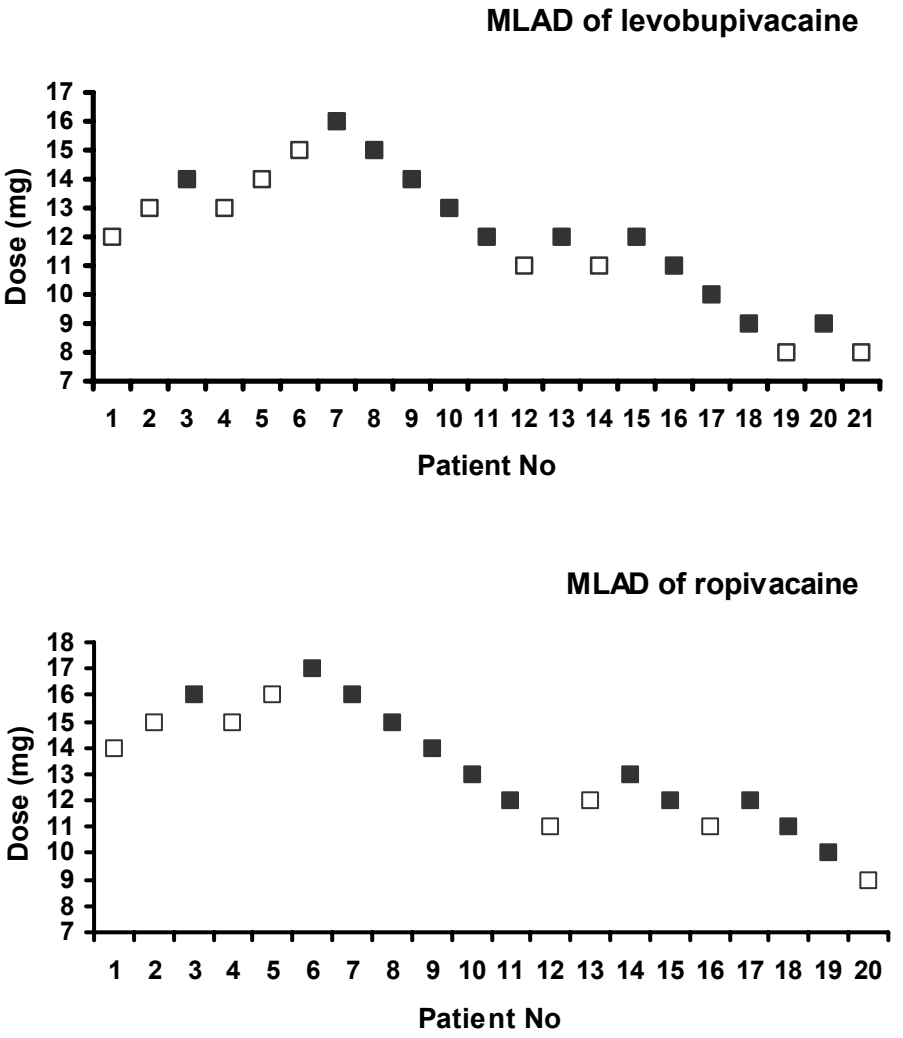

Figure 5. Initial doses of local anaesthetic in individual patients
The initial doses with sufficient (■) and insufficient (□) anaesthesia are shown. The MLAD (95% CI) for levobupivacaine was 11.7 mg (11.1 – 12.4) and for ropivacaine 12.8 mg (12.2 – 13.4).

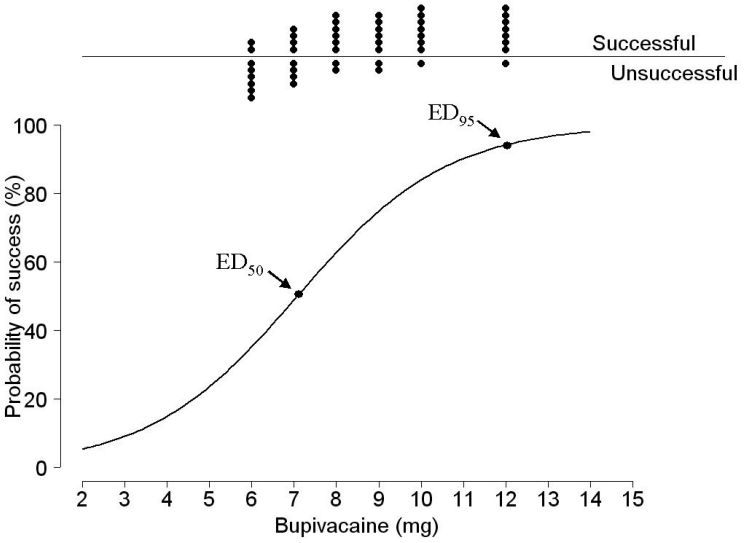

Figure 6. Logistic regression plot to determine ED_{50} (7.1 mg) and ED_{95} (12.3 mg) for isobaric bupivacaine using an intrathecal catheter.

5.5. Intrathecal catheter tip position

The postoperative roentgenograms revealed 30 catheter tip locations in cranial and 14 tip locations in caudal position by the predetermined definition (study IV). Estimated by the logistic model, which includes both the dose and the catheter tip position (up/down) factors, there was neither a statistically significant effect of catheter tip direction ($p = 0.2$) nor statistically significant interaction effect of dose and catheter tip direction ($p = 0.6$) to success.

The puncture level of the spinal catheter was correctly identified in 25 cases (52.1%). In five cases (10.4%) the level of puncture was lower than that estimated by the anaesthetist. The puncture level was one or two spaces higher than thought by the anaesthetist on 18 occasions (37.5%).

5.6. Haemodynamic changes

In study III, nine patients in group L and 11 patients in group R required ephedrine for correction of hypotension during surgery as assessed by the attending anaesthetist. The mean (SD) cumulative dose of ephedrine in study III for those patients who required it was 8 (4) mg. In study IV, eight patients

required ephedrine after anaesthesia induction and a further 11 patients required ephedrine for correction of hypotension during surgery. The mean (SD) cumulative dose of ephedrine for those patients who required it was 18 (15) mg.

5.7. Adverse effects

No major adverse events occurred in any of the patients.

In the observational paper of the review three patients out of 75 developed PDPH. Two patients of study III (one in each group) and one patient of study IV had PDPH of mild severity, which was treated successfully with fluids and NSAIDs. The overall incidence of PDPH was 3.4% (three patients).

6. DISCUSSION

6.1. Methodological aspects

A catheter-over-needle was used in studies I, III and IV. This type of macrocatheter had a tip hole and an additional side hole at 7 mm from the tip providing potentially a more homogeneous distribution of the local anaesthetic in the cerebrospinal fluid (Holst et al. 1998). The catheter was inserted 2.0–2.5 cm into the intrathecal space, which might potentially result in a difference of 5 cm (i.e. approximately one interspace) in the catheter tip position from one patient to another. For the recognition of L3-4 interspace, the Tuffier's line (i.e., an imaginary line drawn between the uppermost iliac crests and believed to mark the L4-5 interspace) has been a guide for lumbar puncture (Vandam, 1989). There is inter-individual variability in predicting the vertebral level of needle and catheter insertion due to anatomic variability of the palpable landmarks (Hogan, 1993). Indeed, evaluation of the intended L3-4 interspace is difficult as indicated by the success rate of only approximately 50% in study IV. Most often the puncture site was higher than expected. The present findings are in accordance with previous studies which have demonstrated inaccuracies in subjects when attempting to identify lumbar interspaces (Broadbent et al. 2000; Hogan, 1993; Van Gessel et al. 1993a).

Surgical anaesthesia was evaluated using pinprick assessment with short-bevel needle and response to transcutaneous tetanic electric stimulation (50 Hz at 60 mA) for five seconds at T12 level on the side of surgery. Pinprick assessment has the advantages of being simple, repeatable and reproducible and can be applied without patient awareness (Lynn and Perl, 1977). Generally, loss of sensation to cold occurs before pinprick, and both of these before touch, each stage correlating with inhibition of C, Aδ and Aβ fibres, respectively (Liu et al. 1995). Transcutaneous electrical stimulation has been shown to provide a stimulus equivalent to surgical incision in studies of minimum alveolar concentration of isoflurane and in studies of spinal anaesthesia with tetracaine (Peterson-Felix et al. 1993; Sakura et al. 2000).

The motor block was assessed by using a modified Bromage scale, where the numerical order is reversed in comparison with the original Bromage scale. This scale is a subjective and qualitative measurement of both spread and the intensity of block in the lower limbs (Bromage, 1965). Grading by the Bromage scale is a rapid and simple method which does not require any special equipment. The Bromage scale concerns the entire leg, which is important in clinical practice. Nevertheless, the Bromage grading gives the location of the motor block unproportional significance, as it emphasizes movements of the foot and toe joints, which require only small amounts of muscle strength. Being simple to perform and easy for the patient, without special equipment, the

modified Bromage scale method offers a reliable method to test the onset and quality of motor block for the surgical procedure.

We defined sufficient anaesthesia for hip replacement surgery as loss of pinprick at T12 dermatome (Schnider et al., 1993). Although anaesthesia level at T10 dermatome has been suggested for hip surgery it might be logic that lower sensory level at T12 dermatome has advantages in respect of haemodynamic stability (Biboulet et al. 1993). The assessment of sensory level at T12 proved appropriate although four patients of twelve in whom anaesthesia was initially sufficient required an additional dose of local anaesthetic to complete surgery in study III. In study IV, the corresponding figure was one of 32.

In study III, there was a difference in the mean MLAD volumes of levobupivacaine (4.68 ml) and ropivacaine (6.4 ml), because of both the dose requirement in milligrams and also the slightly different concentrations of the available commercial formulations. However, previous studies indicate that the total dose of local anaesthetic in milligrams rather than the volume seems to be more important in determining the extent of spinal anaesthesia (Ben-David et al. 1996; Kuusniemi et al. 1999). The total dose also determines the duration of the block (Tarkkila et al. 1997). Thus, the difference in the volume of the study drugs in the present study probably has little or no effect on the extent of the block and the MLADs.

The 20 min assessment time for the block extension possibly did not allow enough time for the maximal effect of the initial dose to be achieved. The clinical time frame did not allow us to assess the local anaesthetic requirements after the first 20 min post drug injection more closely (i.e. in small supplemental local anaesthetic increments). The supplemental doses were administered based on the clinical assessment by the attending anaesthetist who considered the extent of the initial block, patient characteristics as well as the tight time limitations determined by the specific circumstances such as the surgeon and his needs.

Study designs involving dose-varying regimes such as predetermined multiple dose testing and up-and-down sequential allocation have found more informative than fixed recipe designs and allow quantification of effect (Dixon 1965; Lu et al. 2003; Paul and Fisher, 2001). In the studies III and IV, the up-and-down and multiple dose testing method was used, respectively. It is appropriate to concentrate on the MLAD and ED_{50} region, as that dose can guide as initially in using as small doses as possible to patients susceptible to such adverse effects as hypotension and in whom supplemental doses can easily be given utilizing the spinal catheter.

6.2. Clinical aspects

The number of older people over 65 years in Estonia is steadily growing from 11.6% in year 1990 to 16.1% in year 2004 (http://pub.stat.ee). Various factors, such as age, health status, disease process, type and extent of operative procedure, provide differing circumstances, which an anaesthesiologist is obliged to cope with. Therefore the type of anaesthesia may play important role in this context. CSA provides greater haemodynamic stability, control of the duration of anaesthesia and motor block, the possibility of increasing the extent of anaesthesia, and good postoperative analgesia (Sutter et al. 1989; Niemi et al. 1994; Wilhelm et al. 1997; Möllmann et al. 1999).

Haemodynamic stability during perioperative period plays a crucial role in the management of the patient. Various prophylactic and rescue regimens have been advocated for haemodynamic disturbances with emphasis on prevention of hypotension. Prophylactic measures include prehydratation with crystalloid or colloid or administration vasoactive agents (Critchley and Conway, 1996; Sharma et al. 1997; Arndt et al. 1998). A potential means for prophylaxis of hypotension is by manipulation of spinal anaesthesia with unilateral block or with the use small doses of local anaesthetics with or without additives (Klimscha et al 1993; Favarel-Garrigues et al. 1996; Casati et al. 1998a; Ben-David et al. 2000; Kuusniemi et al. 2000). The ability to titrate small doses of local anaesthetics is beneficial in the hemodynamically compromised patient, such as in the elderly or in those with cardiovascular diseases (Klimscha et al 1993; Schnider et al. 1993; Favarel-Garrigues et al. 1996).

The previously reported dose of isobaric levobupivacaine for single-shot spinal anaesthesia for hip replacement surgery is 17.5 mg, and for isobaric ropivacaine doses 17.5–25 mg have been used (McNamee et al. 2001; Glaser et al. 2002; McNamee et al. 2002). In study III, the MLAD for levobupivacaine was 11.7 mg and that of ropivacaine 12.8 mg. The mean total doses of LA required to complete surgery in our study are somewhat lower, though in the range of those reported earlier and higher than the calculated MLAD. However, the small numerical difference (1.1 mg) in the MLADs does not allow us to make the interpretation that levobupivacaine would be more potent than ropivacaine, as the 95% confidence intervals overlap.

Doses of 5–30 mg of isobaric bupivacaine have been reported to be required for hip replacement surgery (Pitkänen et al. 1992a; Biboulet et al. 1993). In the study IV, the ED_{50} and ED_{95} for isobaric bupivacaine were 7.1 mg and 12.3 mg. The mean total dose of bupivacaine (10 mg) required to complete surgery in our study is lower than the calculated ED_{95}. These small doses can guide us in the assessment of combined doses when small doses would be of importance. Use of small doses of local anaesthetic allows also better control of the duration of spinal anaesthesia (Tarkkila et al. 1997). Although supplementation was

sometimes required it was always easy to administer via the spinal catheter indicating the feasibility of this method.

We were not interested to determine the ED_{100} of local anaesthetic in CSA. We assume that the local anaesthetic dose requirements more or less follow the normal distribution. Thus, determining ED_{100} and letting that guide us in administering local anaesthetics to patients in whom all e.g. haemodynamic adverse effects are to be avoided, would lead to significant over-shooting in dosing. This can easily be demonstrated if normal distribution and a dose-response curve are drawn on a single figure (Sonner, 2002). On the other hand, determination of ED_{100} would be important when single shot spinal anaesthetic technique is used.

Also the direction, which the catheter tip takes upon insertion, may have affected the results of study III as we were not able to define the catheter tip position in that study. It has been shown that in patients with cranially running microcathers or catheters with the tip at the level of the puncture site, the onset of analgesia was faster and the required doses of local anaesthetics were smaller than in patients with caudally running catheters (Standl and Beck, 1994). This finding is in contrast to those of a previous study with hypobaric bupivacaine or tetracaine, where no correlation was found between the level of the tip of the 20-gauge catheter with three side ports and the achieved sensory level (Van Gessel et al. 1993a). It seems that the longer the catheter is advanced in to the intrathecal space the likelihood of caudal direction increases: microcatheters inserted in patients in a lateral position and introduced more than 4 cm into subarachnoid space had a higher incidence of being placed caudally compared with for those inserted less than 4 cm, although such relationship was not observed in our earlier study (Standl and Beck, 1994; Sell et al. 1999). In addition, if directional needle for microcatheter insertion was used, a high proportion of catheters will take a cranial direction (Standl et al. 1995). In the present study IV, we used the postoperative roentgenograms to reveal catheter tip locations in the subarachnoid space. Still, only in 68% of patients the catheter tip was in cranial position per our definition (over the lower margin of third lumbar vertebra). However, based on our result, the catheter tip position may not play a significant role after all in determining the extent of the block.

We did not see any major haemodynamic adverse effects. 39 patients out of 89 patients needed vasopressors in our series while 15 patients out of 89 patients required ephedrine for correction of hypotension during induction of anaesthesia by the attending anaesthetist. Further doses of ephedrine were required in some patients to treat hypotension occurring in association with blood loss.

In studies III and IV, the over-all incidence of PDPH was 3.4%. A similar incidence (4%) was found in our previous study (Sell et al. 1997). The relatively low incidence of PDPH in our series might be partly explained with the fact that this new type of catheter causes less trauma to the dura mater

compared to microcatheter use (Holst et al. 1998). This is in accordance with earlier studies with a spinal macrocatheter (Denny et al. 1987; Hurley and Lambert 1990; Liu et al. 1993; Mazze and Fujinaga 1993; De Andres et al. 1994; Standl et al. 1995a; Van Gessel et al. 1995; Möllmann et al. 1996). The theoretical advantage of this system is that the hole in the dura has the same size as the catheter, thus minimizing the CSF leak and the rate of postdural puncture headache (Möllmann et al. 1996). However, in elderly patients the risk for PDPH is small and therefore CSA can be used routinely for major orthopaedic surgery.

Recently, the frequency of PDPH with use of catheter through-needle technique and the catheter over-needle technique has been studied in young healthy volunteers. In spite of high overall incidence of PDPH (78%) the over-needle group has shown a significantly shorter duration of PDPH and lower maximum pain intensity than the through-needle group (Gosch et al. 2005).

None of the patients reported signs of neurotoxicity such as cauda equina syndrome. Potential neurotoxicity related to the use of intrathecal catheters has recently become a concern because of reports of cauda equina syndrome. Most published cases have been associated with the use of 5% lidocaine in hyperbaric (7.5%) dextrose (Ilias et al., 1998). Unfortunately, only a few prospective studies have investigated the real incidence of neurological complications (Horlocker et al. 1997) The sample size in the present studies is too small to allow us to state that isobaric levobupivacaine, ropivacaine and bupivacaine via CSA would be safer than lidocaine in this respect. Thus, neurological symptoms have to be surveyed carefully in all patients in whom the CSA technique is used until further evidence is available.

7. CONCLUSIONS

1. The clinical characteristics, based on our previous observational studies, of the used catheter-over-needle technique were reviewed.
2. Of the available methods the up-and-down method yields relatively good estimates of ED_{50} in the case of small and very small sample sizes. This method is simple to implement but it can cause problems with bias of ED_{50} estimator, depending on the starting level of dosage and assumed value of δ, which reflects the variability of response across doses. The logit model for estimating ED_{50} may be preferred because of existence standard statistical software.
3. The determined MLAD of isobaric levobupivacaine was 11.7 mg and that of ropivacaine 12.8 mg in CSA for hip replacement surgery.
4. The determined ED_{50} and ED_{95} of isobaric bupivacaine were 7.1 mg and 12.3 mg in CSA for hip replacement surgery.
5. The location of the tip of the intrathecal catheter had no effect of isobaric bupivacaine requirements.

8. REFERENCES

Alley EA, Kopacz DJ, McDonald SB, Liu SS. Hyperbaric spinal levobupivacaine: a comparison to racemic bupivacaine in volunteers. Anesth Analg 2002; 94: 188–93

Anderson L, Walker J, Brydon C, Serpell MG. Rate of injection through whitacre needles affects distribution of spinal anaesthesia. Br J Anaesth 2001; 86: 245–8

Arkoosh VA, Aluru D, Buxbaum JL, Leighton BL. Intrathecal bupivacaine dose-response in multiparous patients receiving oxytocin. Proc SOAP. Anesthesiology 1999; 90: A66

Arndt JO, Bomer W, Krauth J, Marquardt B. Incidence and time course of cardiovascular side effects during spinal anesthesia after prophylactic administration of intravenous fluids or vasoconstrictors. Anesth Analg 1998; 87: 347–54

Atchison SR, Wedel DJ, Wilson PR. Effect of injection rate on level and duration of hypobaric spinal anesthesia. Anesth Analg 1989; 69: 496–500

Ben-David B, Levin H, Solomon E, Admoni H, Vaida S. Spinal bupivacaine in ambulatory surgery: the effect of saline dilution. Anesth Analg 1996; 83: 716–20

Ben-David B, Frankel R, Arzumonov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. Anesthesiology 2000; 92: 6–10

Bengtsson M, Malmquist L-A, Edström HH. Spinal analgesia with glucose-free bupivacaine: effects of volume and concentration. Acta Anaesthesiol Scand 1984; 28: 583–6

Berde CB, Strichartz GR. Local anaesthetics. In: Miller RD, ed. Anesthesia. 5th Edn. Philadelphia: Churcill-Livingstone, 2000; 491–521

Biboulet P, Deschodt J, Aubas P, Vacher E, Chauvet P, D'Athis F. Continuous spinal anesthesia: does low-dose plain or hyperbaric bupivacaine allow the performance of hip surgery in elderly? Reg Anesth 1993; 18: 170–5

Biboulet P, Capdevila X, Aubas P, Rubenovitch J, Deschodt J, d'Athis F. Causes and prediction of maldistribution during continuous spinal anesthesia with isobaric or hyperbaric bupivacaine. Anesthesiology 1998; 88: 1487–94

Bier A. Versuche über Cocainisirung des Rückenmarkes. Dtsche Z Chir 1899; 51: 361–9

Bizzari D. Continuous spinal anesthesia, using a special needle and catheter. Anesth Analg 1964; 43: 393–9

Blomquist H, Nilsson A, Arweström E. Spinal anesthesia with 15 mg bupivacaine 0.25% and 0.5%. Reg Anest 1988; 13: 165–8

Bodily MN, Carpenter RL, Owens BD. Lidocaine 0.5% spinal anaesthesia: a hypobaric solution for short-stay perirectal surgery. Can J Anaesth 1992; 39: 770–3

Bridenbaugh PO, Greene NM, Brul SJ. Spinal (subarachnoid) neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain, 3rd Edn. Philadelphia: Lippincott-Raven Publishers, 1998; 203–41

Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell R. Ability of anaesthetists to identify a marked lumbar interspace. Anaesthesia 2000; 55: 1122–6

Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965; 16(Suppl): 55–69

Brownlee KA, Hodges JL, Rosenblatt M. The up-and-down method with small samples. Am Stat Assoc J 1953; 48: 262–77

Bucx MJ, Kroon JW, Stienstra R. Effect of speed of injection on the maximum sensory level for spinal anesthesia using plain bupivacaine 0.5% at room temperature. Reg Anesth 1993; 18: 103–5

Burgess FW, Woiwood MD, Lutz RL, Walz EJ Jr, Perkins DE. Continuous spinal anesthesia with hyperbaric bupivacaine: a dose-response analysis. Reg Anest 1991; 16: 52–6

Cameron AE, Arnold RW, Ghorisa MW, Jamieson V. Spinal analgesia using bupivacaine 0.5% plain. Variation in the extent of the block with patient age. Anaesthesia 1981; 36: 318–22

Camorcia M, Capogna G, Columb MO. Minimum local analgesic doses of ropivacaine, levobupivacaine, and bupivacaine for intrathecal labor analgesia. Anesthesiology 2005; 102: 646–50

Carpenter RL, Hogan QH, Liu SS, Crane B, Moore J. Lumbosacral cerebrospinal fluid volume is the primary determinant of sensory block extent and duration during spinal anesthesia. Anesthesiology 1998; 89: 24–9

Carvalho B, Durbin M, Drover DR, Cohen SE, Ginosar Y, Riley ET. The ED50 and ED95 of Intrathecal Isobaric Bupivacaine with Opioids for Cesarean Delivery. Anesthesiology 2005; 103: 606–12

Casati A, Fanelli G, Beccaria P, Leoni A, Berti M, Senatore R, Torri G. Block distribution and cardiovascular effects of unilateral spinal anaesthesia by 0.5% hyperbaric bupivacaine: A clinical comparison with bilateral spinal block. Minerva Anestesiol 1998a; 64: 307–12

Casati A, Fanelli G, Cappelleri G, Leoni A, Berti M, Aldegheri G, Torri G. Does speed of intrathecal injection affect the distribution of 0.5% hyperbaric bupivacaine? Br J Anaesth 1998b; 81: 355–7

Chan VWS, Peng P, Chinyanga H, Lazarou S, Weinbren J, Kaszas Z. Determining minimum effective anesthetic concentration of hyperbaric bupivacaine for spinal anesthesia. Anesth Analg 2000; 90:1135–40

Choi SC. An investigation of Wetherill's method of estimation for the up-and-down experiment. Biometrics 1971; 27: 961–70

Glaser C, Marhofer P, Zimpfer G, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg 2002; 94: 194–8

Cohen S, Amar D, Panttuck EJ, Singer N, Divon M. Decreased incidence of headache after accidental dural puncture in caesarean delivery patients receiving continuous intrathecal anaesthesia. Acta Anaesthesiol Scand 1994; 38: 716–8

Collard CD, Eappen S, Lynch EP, Concepcion M. Continuous spinal anesthesia with invasive hemodynamic monitoring for surgical repair of the hip in two patients with severe aortic stenosis. Anesth Analg 1995; 81: 195–8

Columb MO, Lyons G. Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. Anesth Analg 1995; 81: 833–7

Columb MO, Thomson HE. Correspondence: confidence with confidence intervals. Br J Anaesth 2005; 95: 111–2

Critchley LA, Conway F. Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol. Br J Anaesth 1996; 76: 734–6
Curbello MM. Continuous peridural segmental anesthesia by means of a urethral catheter. Current Research in Anesthesiology 1949; 28:13–6
Danelli G, Zangrillo A, Nucera D, Giorgi E, Fanelli G, Senatore R, Casati A. The minimum effective dose of 0.5% hyperbaric spinal bupivacaine for cesarean section. Minerva Anesthesiol 2001; 67: 573–7
D'Angelo R, Nelson KE; Meister G, Gaver R, Eisenach JC. Dose response study of spinal fentanyl in early labor. Proc SOAP. Anesthesiology 1998; 89: A17
Davis H, King WR. Densities of common spinal anesthetic solutions at body temperature. Anesthesiology 1952; 13: 184–8
Davis H, King WR. Densities of cerebrospinal fluid of human beings. Anesthesiology 1954; 15: 666–72
De Andres J, Bellver J, Bolinches R. Comparison of continuous spinal anaesthesia using 32-gauge catheter with anaesthesia using a single dose 24-gauge atraumatic needle in young patients. Br J Anaesth 1994; 73: 747–50
De Andres J, Valia JC, Olivares A, Beliver J. Continuous spinal anestheisa: a comparative study of a standard microcatheter and Spinocath. Reg Anesth Pain Med 1999; 24: 110–6
Dean HP. The importance of anaesthesia by lumbar injections in operations for acute abdominal disease. BMJ 1906; 1: 1086–90
de Jong RH, Eger EI. MAC expanded: AD_{50} and AD_{95} values of common inhalation anesthetics in man. Anesthesiology 1975; 42: 384–9
Denny NM, Masters R, Pearson D, Read J, Sihota M, Selander DE. Postural puncture headache after continuous spinal anesthesia. Anesth Anlg 1987; 66: 791–4.
Denny NM, Selander DE. Continuous spinal anaesthesia. Br J Anaesth 1998; 81: 590–7
Dixon WJ, Mood AM. A method for obtaining and analyzing sensitivity data. Am Stat Assoc J 1948; 43: 109–26
Dixon WJ. The up-and-down method for small samples. Am Stat Assoc J 1965; 60: 967–78
Döbler K, Nolte H. Are the density of cerebrospinal fluid and the extent of isobaric spinal anesthesia influenced by elevated glucose concentration in blood and cerebrospinal fluid or others factors? Reg Anaesth 1990; 13: 101–7
Drasner K. Models for local anesthetic toxicity from continuous spinal anesthesia. Reg Anesth 1993; 18: 434–8
Dripps RD. A comparison of the malleable needle and catheter techniques for continuous spinal anesthesia. N York J Med 1950; 50: 1595–9
Dripps RD. Long-term follow-up of patients who received 10,098 spinal anesthetics. JAMA 1954; 156: 1486–91
Ernst EA. In-vitro changes of osmolality and density of spinal anesthetic solutions. Anesthesiology 1968; 29: 104–9
Ellis H, Feldman S, Harrop-Griffiths W. Anatomy for anaesthetists. 8th Edn. Oxford, Blacwell Publishing Ltd, 2004: 119–46
Enzmann DR, Pelc NJ. Normal flow patterns of intracranial and spinal cerebrospinal fluid defined with phase-contrast cine MR imaging. Radiology 1991; 178: 467–74
Favarel-Garrigues JF, Sztark F, Petitjean ME, Thicoipe M, Lassie P, Dabadie P. Hemodynamic effects of spinal anesthesia in the elderly: single dose versus titration through a catheter. Anesth Analg 1996; 82: 312–6

FDA Safety alert. Cauda equina syndrome associated with use of small-bore catheters in continuous spinal anesthesia. May 29, 1992

Flaatten H, Felthaus J, Kuwelker M, Wisborg T. Postural post-dural puncture headache. A prospective randomised study and a meta-analysis comparing two different 0.40 mm O.D. (27 g) spinal needles. Acta Anaesthesiol Scand. 2000; 44: 643–7

Frawley GP, Farrell T, Smith S. Levobupivacaine spinal anesthesia in neonates: a dose range finding study. Pediatr Anesth 2004; 14: 838–44

Gaggero G, Van Gessel E, Forster A, Gosteli P, Gamulin Z. Comparison of 5 mg tetracaine diluted in 1 ml, 2 ml and 4 ml of 10% glucose for spinal anesthesia. Acta Anaesthesiol Scand 1993; 37: 697–701

Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED_{50} and ED_{95} of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. Anesthesiology 2004; 100: 676–82

Glaser C, Marhofer P, Zimpfer G, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg 2002; 94: 194–8

Gosch UW, Hueppe M, Hallschmid M, Born J, Schmucker P, Meier T. Post-dural puncture headache in young adults: comparison of two small-gauge spinal catheters with different needle design. Br J Anaesth 2005; 94: 657–61

Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985; 64: 715–30

Greitz D, Franck A, Nordell B. On the pulsatile nature of intracranial and spinal CSF-circulation demonstrated by MR imaging. Acta Radiol 1993; 34: 321–8

Hallworth SP, Fernando R, Columb MO, Stocks GM. The effect of posture and baricity on the spread of intrathecal bupivacaine for elective cesarean delivery. Anesth Analg 2005; 100: 1159–65

Hammock MK, Milhorat TH. The cerebrospinal fluid: current concepts of its formation. Ann Clin Lab Sci 1976; 6: 22–6

Henry-Feugeas MC, Idy-Peretti I, Baledent O, Poncelet-Didon A, Zannoli G, Bittoun J, Schouman-Claeys E. Origin of subarachnoid cerebrospinal fluid pulsations: a phase-contrast MR analysis. Magn Reson Imaging 2000; 18: 387–95

Higuchi H, Hirata J, Adachi Y, Kazama T. Influence of lumbosacral cerebrospinal fluid density, velocity, and volume on extent and duration of plain bupivacaine spinal anesthesia. Anesthesiology 2004; 100: 106–14

Hirabayashi Y, Igarashi T, Suzuki H, Fukuda H, Saitoh K, Seo N. Mechanical effects of leg position on vertebral structures examined by magnetic resonance imaging. Reg Anest Pain Med 2002; 27: 429–32

Hsi BP. The multiple sample up-and-down method in bioassay. Am Stat Assoc J 1969; 64: 147–62

Hocking G, Wildsmith JAW. Intrathecal drug spread. Br J Anaesth 2004; 93: 568–78

Hogan Q. Tuffier's line: the normal distribution of anatomic parameters. Anesth Analg 1993; 78: 194–5

Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L. Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure. Anesthesiology 1996; 84: 1341–9

Hogan Q. Gross anatomy of the human vertebral column. In: Yaksh TL, ed. Spinal drug delivery. Amsterdam, The Netherlands: Elsvier Science B.V., 1999: 97–113

Holst D, Möllmann M, Scheuch E, Meissner K, Wendt M. Intrathecal local anesthetic distribution with the new Spinocath catheter. Reg Anesth Pain Med 1998; 23: 463–8

Horlocker TT, Wedel DJ, Wilson PR. Effect of injection rate on sensory level and duration of hypobaric bupivacaine spinal anesthesia for total hip arthroplasty. Anesth Analg 1994; 79: 773–7

Horlocker TT, McGregor DG, Matsushige DK, Chantigian RC, Schroeder DR, Besse JA. Neurologic complications of 603 consecutive continuous spinal anesthetics using macrocatheter and microcatheter techniques. Anesth Analg 1997; 84: 1063–70

http://pub.stat.ee/pxweb.2001/Database/Rahvastik/01Rahvastikunaitajad_ja_koosseis/04Rahvaarv_ja_rahvastiku_koosseis/04Rahvaarv_ja_rahvastiku_koosseis.asp

Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 1998; 86: 797–804

Hurley RJ, Lambert DH. Continuous spinal anaesthesia with a microcatheter technigue. Reg Anest 1987; 12: 54–8

Hurley RJ, Lambert DH. Continuous spinal anaesthesia with a microcatheter technigue: preliminary experience. Anesth Analg 1990; 70: 97–102

Ilias WK, Klimscha W, Skrbensky G, Weinstabl R, Widhalm A. Continuous microspinal anaesthesia: another perspective on mechanisms inducing cauda equina syndrome. Anaesthesia 1998; 53: 618–23

Janik R, Dick W, Stanton-Hicks M. The effect of the injection speed on the blockade characteristics of hyperbaric bupivacaine and tetracaine in spinal anesthesia. Reg Anaest 1989; 12: 63–8

Jørgensen LN, Rasmussen LS, Nielsen PT, Leffers A, Albrecht-Beste E. Anti-thrombotic efficacy of continuous epidural analgesia following knee replacement. Br J Anaesth 1991; 66: 8–12

Juelsgaard P, Sand NP, Felsby S, Dalsgaard J, Jakobsen KB, Brink O, Carlsson PS, Thygesen K. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. Eur J Anaesthesiol 1998; 15: 656–63

Kanai A, HirumaH, Katakura T, Sase S, Kawakami T, Hoka S. Low-concentration lidocaine rapidly inhibits axonal transport in cultured mouse dorsal root ganglion neurons. Anesthesiology 2001; 95: 675–80

Kasaba T, Onizuka S, Takasaki M. Procaine and mepivacaine have less toxicity in vitro than other clinically used local anesthetics. Anesth Analg 2003, 97: 85–90

Kehlet H. Postoperative pain relief-what is the issue? (Editorial). Br J Anaest 1994; 72: 375–8

Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Briedenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: Lippincott, 1998: 129–75

Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002; 183: 630–4

Kershaw CD. A comparison of estimators of the ED50 in up-and-down experiments. J Stat Comput Sim 1987; 27: 175–84

King HK, Wooten DJ, Effects of drug dose, volume, and concentration on spinal anesthesia with isobaric tetracaine. Reg Anesth 1995; 20: 45–9

Klimscha W, Weinstabl C, Ilias W, et al. Continuous spinal anesthesia with microcatheter and low-dose bupivacaine decreases the hemodynamic effects of centroneuraxis blocks in elderly patients. Anesth Analg 1993; 77: 275–80

Knudsen K, Beckman Suurküla M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997; 78: 507–14

Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg 2000; 90: 642–8

Korhonen AM, Valanne JV, Jokela RM, Ravaska P, Volmanen P, Korttila K. Influence of the injection site (L2/3 or L3/4) and the posture of the vertebral column on selective spinal anesthesia for ambulatory knee arthroscopy. Acta Anaesthesiol Scand 2005; 49: 72–7

Kuusniemi KS, Pihlajamäki KK, Pitkänen MT, Korkeila JE. Low-dose bupivacaine: a comparison of hypobaric and near isobaric solutions for arthroscopic surgery of the knee. Anaesthesia 1999; 54: 540–5

Kuusniemi KS, Pihlajamäki KK, Pitkänen MT, Korkeila JE. Low-dose bupivacaine: a comparison of hypobaric and near isobaric solutions for arthroscopic surgery of the knee. Reg Anesth Pain Med 2000; 25: 605–10

Labaille L, Benhamou D, Westerman J. Hemodynamic effects of continuous spinal anesthesia: a comparative study between low and high doses of bupivacaine. Reg Anest 1992; 17: 193–6

Lacassie HJ, Millar S, Leithe LG, Muir HA, Montana R, Poblete A, Habib AS. Dural ectasia: a likely cause of inadequate spinal anaesthesia in two parturients with Marfan's syndrome. Br J Anaesth 2005; 94: 500–4

Lemmon WT. A method for continuous spinal anesthesia. Ann Surg 1940; 111:144

Little RE. A mean square error comparison of certain median response estimates for the up-and-down method with small samples. Am Stat Assoc J 1974; 69: 202–6

Liu N, Montefiore A, Kermarec N, Rauss A, Bonnet F. Prolonged placement of spinal catheters does not prevent postural puncture headache. Reg Anesth 1993; 18: 110–3

Liu S, Kopacz DJ, Carpenter RL. Quantitative assessment of differential sensory nerve block after lidocaine spinal anesthesia. Anesth Analg 1995; 82: 60–3

Lu W, Ramsay JG, Bailey JM. Reliability of pharmacodynamic analysis by logistic regression: mixed-effects modeling. Anesthesiology 2003; 99: 1255–62

Lui ACP, Polis TZ, Cicutti NJ. Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. Can J Anaesth 1998; 45: 297–303

Lynn B, Perl ER. A comparison of four tests for assessing the pain sensitivity of different subjects and test areas. Pain 1977; 3: 353–65

Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. Br J Anaesth 1998; 81: 899–901

Mahisekar UL, Winnie AP, Vasireddy AR, Masters RW. Continuous spinal anesthesia and post dural puncture headache: a retrospective study. Reg Anesth 1991; 16: 107–11

Malinovsky, JM, Charles F, Baudrimont M, Pereon Y, Le Corre , Pinaud M, Benhamou D. Intrathecal ropivacaine in rabbits: pharmacodynamic and neurotoxicologic study. Anesthesiology 2002; 97: 429–35

Manica VS, Bader AM, Fragneto R, Gilbertson L, Datta S. Anesthesia for in vitro fertilization: a comparison of 1.5% and 5% spinal lidocaine for ultrasonically guided oocyte retrieval. Anesth Analg 1993; 77: 453–6

Mardirosoff C, Dumont L, Lemedioni P, Pauwels P, Massaut J. Sensory block extension during combined spinal and epidural. Reg Anesth Pain Med 1998; 23: 92–5

Mazze RI, Fujinaga M. Postural puncture headache after continuous spinal anesthesia with 18G and 20G needles. Reg Anesth 1993, 18: 447–51

McClure JH, Brown DT, Wildsmith JAW. Effect of injected volume and speed of injection on the spread of spinal anaesthesia with isobaric amethocaine. Br J Anaesth 1982; 54: 917–20

McNamee DA, Parks L, McClelland AM, et al. Intrathecal ropivacaine for total hip arthroplasty: double-blind comparative study with isobaric 7.5 mg ml^{-1} and 10 mg ml^{-1} solutions. Br J Anaesth 2001; 87: 743–7

McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery. Br J Anaesth 2002; 89: 702–6

Modig J, Borg T, Karlstrom G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. Anesth Analg 1983; 62: 174–80

Möllmann M, Van Steenberge A, Sell A, Pitkänen M, Holst D, Van Dongen A, Berg S. Spinocath, a new approach to continuous spinal anaesthesia–Preliminary results of a multicenter trial. Int Monit Reg Anaesth 1996; 3: 74

Möllmann M, Cord S, Holst D, Auf der Landwehr U. Continuous spinal anaesthesia or continuous epidural anaesthesia for post-operative pain control after hip replacement? Eur J Anaesth 1999; 16: 454–61

Morrison S, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. Anesth Analg 2000; 90: 1308–14

Mukkada TA, Bridenbaugh PO, Singh P, Edström HH. Effects of dose, volume and concentration of glucose-free bupivacine in spinal anesthesia Reg Anest 1986; 11: 98–101

Muralidhar V, Kaul I-IL, Mallick P. Over-the-needle versus microcathetr-through-needle technique for continuous spinal anesthesia: A preliminary study. Reg Anesth Pain Med 1999; 24: 417–21

Neigh JL, Kane PB, Smith TC. Effects of speed and direction of injection on the level and duration of spinal anesthesia. Anesth Analg 1970; 49: 912–6

Nielssen TH, Kristoffersen E, Olsen KH, Larsen HV, Husegaard HC, Wernberg M. Plain bupivacaine 0.5% or 0.25% for spinal analgesia? Br J Anaesth 1989; 62: 164–7

Niemi L, Tuominen M, Pitkänen M, Rosenberg PH. Effect of late posture change on the level of spinal anaesthesia with plain bupivacaine. Br J Anaesth 1993; 71: 807–9

Niemi L, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems and side effects associated with continuous intrathecal or epidural post-operative analgesia in patients undergoing hip arthroplasty. Eur J Anaesthesiol 1994; 11: 469–74

Paul M, Fisher DM. Are estimates of MAC reliable? Anesthesiology 2001; 95: 1362–70

Peng PWH, Chan VWS, Perlas A. Minimum effective anaesthetic concentration of hyperbaric lidocaine for spinal anaesthesia. Can J Anaesth 1998; 45: 122–9

Peterson-Felix S, Zbinden AM, Fischer M, Thomson DA. Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. Anesthesiology 1993; 79: 959–65

Petros AJ, Barnard M, Smith D, Ronzoni G. Continuous spinal anesthesia: dose requirements and characteristics of the block. Reg Anesth 1993; 18: 52–4

Pitkänen M, Haapaniemi L, Tuominen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 1984; 56: 279–84

Pitkänen M. Body mass and spread of spinal anesthesia. Anesth Analg 1987; 66: 127–31

Pitkänen M, Rosenberg R, Silvanto M, Tuominen M. Haemodynamic changes during spinal anaesthesia with slow continuous infusion or single dose of plain bupivacaine. Acta Anaesthesiol Scand 1992a; 36: 526–9

Pitkänen M, Tuominen M, Rosenberg P, Wahlström T. Technical and light microscopic comparison of four different small-diameter catheters used for continuous spinal anaesthesia. Reg Anesth 1992b; 17: 288–91

Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJM. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: Implications for therapeutic indexes. Anesthesiology 1999; 90: 944–50

Povey HMR, Jacobsen J, Westergaard-Nielsen J. Subarachnoid analgesia with hyperbaric 0.5% bupivacaine: effect of a 60-min period in sitting. Acta Anaesthesiol Scand 1989; 33: 295–7

Racle JP, Benkhadra A, Poy JY, Fockenier F. Spinal analgesia with hyperbaric bupivacaine: influence of age. Br J Anaesth 1988; 60: 508–14

Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal JA, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT; ISPOCD2 (International Study of Postoperative Cognitive Dysfunction) Investigators. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47: 260–6

Ready LB, Plumer MH, Haschke RH, Austin E, Sumi SM. Neurotoxicity of intrathecal local anesthetics in rabbits. Anesthesiology 1985; 63: 364–70

Richardson MG, Wissler RN. Density of cerebrospinal fluid in pregnant and nonpregnant humans. Anesthesiology 1996; 85: 326–30

Rigler ML, Drasner K, Krejcie TC, Yelish SJ, Scholnick FT, Defontes J, Bohner D. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991; 72: 275–81

Robson SC, Samsoon G, Boys RJ, Rodeck C, Morgan B. Incremental spinal anaesthesia for elective caesarean section: maternal and fetal haemodynamic effects. Br J Anaesth 1993; 70: 634–8

Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1–12

Sakura S, Sakaguchi Y, Shinzawa M, Hara K, Saito Y. The assessment of dermatomal level of surgical anesthesia after spinal tetracaine. Anesth Analg 2000; 90: 1406–10

Sakura S, Sumi M, Morimoto M, Yamamori Y, Saito Y. Spinal anesthesia with tetracaine in 0.75% glucose: influence of the vertebral interspace used for injection. Reg Anesth Pain Med 1998; 23: 170–5

Sanderson P, Read J, Littlewood DG, McKeown D, Wildsmith JA. Interaction between baricity (glucose concentration) and other factors influencing intrathecal drug spread. Br J Anaesth 1994; 73: 744–6

Saravanan S, Robinson APC, Qayoum Dar A, Columb MO, Lyons GR. Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. Br J Anaesth 2003; 91: 368–72

Schell RM, Brauer FS, Cole DJ, Applegate RL. Persistent sacral nerve root defects after continuous spinal anaesthesia. Can J Anaesth 1991; 38: 908–11

Schiffer E, Van Gessel E, Gamulin Z. Influence of sex in cerebrospinal fluid density in adults. Br J Anaesth 1999; 83: 943–4

Schiffer E, Van Gessel E, Fournier R, Weber A, Gamulin Z. Cerebrospinal fluid density influences extent of plain bupivacaine spinal anesthesia. Anesthesiology 2002; 96: 1325–30

Schnider W. Mueller-Duysing S, Johr M, Gerber H. Incremental dosing versus single-dose spinal anesthesia and hemodynamic stability. Anesth Analg 1993; 77: 1174–8

Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989; 69: 563–9

Sell A, Telnova E, Sõrmus A, Abram M, Mitt U, Van Steenberge A, Samarütel J. Continuous spinal anaesthesia with "Spinocath" technique. Int Monit Reg Anaesth 1997; 9: 65

Sell A, Karjagin J, Avlassevitch D, Laisaar V, Samarütel J. The intrathecal position of “Spinocath” catheters in continuous spinal anaesthesia. Int Monit Reg Anaesth 1999; 3: 55

Sell A, Olkkola KT, Jalonen J, Aantaa R. Correspondence: minimum effective local anaesthetic dose for spinal anaesthesia. Br J Anaesth 2005; 94: 865–6

Sharma SK, Gajraj NM, Sidawi JE. Prevention of hypotension during spinal anesthesia: A comparison of intravascular administration of hetastarch versus lactated Ringer's solution. Anesth Analg 1997; 84: 111–4

Sheskey MC, Rocco AG, Bizzari-Schmid M, Francis DM, Edström H, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. Anesth Analg 1983; 62: 931–5

Silvanto M, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems associated with the use of 32-gauge and 22-gauge spinal catheters. Acta Anaesthesiol Scand 1992; 36: 295–9

Sonner JM. Issues in the design and interpretation of minimum alveolar anesthetic concentration (MAC) studies. Anesth Analg 2002; 95: 609–14

Standl T, Beck H. Influence of the subarachnoid position of microcatheters on onset of analgesia and dose of plain bupivacaine 0.5% in continuous spinal anesthesia. Reg Anesth 1994; 19: 231–6

Standl T, Beck H. Radiological examination of the intrathecal catheter position of microcatheters in continuous spinal anaesthesia. Br J Anaesth 1993; 71: 803–6

Standl T, Eckert S, Rundshagen I, Schulte am Esch J. A directional needle improves effectiveness and reduces complications of microcatheter continuous spinal anaesthesia. Can J Anaesth 1995; 42: 701–5

Standl T, Eckert S, Schulte am Esch J. Microcatheter continuous spinal anaesthesia in the post-operative period: a prospective study of its effectiveness and complications. Eur J Anaesthesiol 1995a; 12: 273–9

Stienstra R, Van Poorten F, Kroon JW. Needle direction affects the sensory level of spinal anesthesia. Anesth Analg 1989; 68: 497–500

Stienstra R, Van Poorten F. Speed of injection does not affect subarachnoid distribution of plain bupivacaine 0.5%. Reg Anesth 1990; 15: 208–10

Stienstra R, Greene NM. Factors affecting the subarachnoid spread of local anaesthetic solutions. Reg Anesth 1991; 16: 1–6

Stienstra R, Dilrosun-Alhadi BZ, Dahan A, van Kleef JW, Veering BT, Burm AG. The epidural "top-up" in combined spinal-epidural anesthesia: the effect of volume versus dose. Anesth Analg 1999; 88: 810–4

Stocks GM, Hallworth SP, Fernando R, England AJ, Columb MO, Lyons G. Minimum local analgesic dose of intrathecal bupivacaine in labor and the effect of intrathecal fentanyl. Anesthesiology 2001; 94: 593–8

Sutter PA, Gamulin Z, Forster A. Comparison of continuous spinal and continuous epidural anaesthesia for lower limb surgery in elderly patients. A retrospective study. Anaesthesia 1989; 44: 47–50

Taivainen T, Tuominen M, Rosenberg PH. Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3-4 or L4-5 interspace. Br J Anaesth 1990; 64: 542–6

Takiguchi T, Okano T, Egawa H, Okubo Y, Saito K, Kitajima T. The effect of epidural saline injection on analgesic level during combined spinal and epidural anesthesia assessed clinically and myelographically. Anesth Analg 1997; 85: 1097–100

Tarkkila P, Huhtala J, Tuominen M. Home-readiness after spinal anaesthesia with small doses of hyperbaric 0.5% bupivacaine. Anaesthesia 1997; 52: 1157–60

Tsutakawa RK. Asymptotic properties of the block up-and-down method in bio-assay. Ann Math Stat 1967*;* 38: 1822–8

Tuohy EB. Continuous spinal anesthesia, its usefulness and technique involved. Anesthesiology 1944; 5: 142–8

Tuohy EB. Continuous spinal anesthesia: A new method of utilizing ureteral catheter. Surgery Clinics of North America 1945; 25: 834–40

Tuominen M, Taivanen T, Rosenberg PH. Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection. Br J Anaesth 1989; 62: 358–61

Tuominen M, Pitkänen M, Rosenberg PH. Effect of speed of injection of 0.5% plain bupivacaine on the spread of spinal anaesthesia. Br J Anaesth 1992; 69: 148–9

Urmey WF, Stanton J, Bassin P, Sharrock NE. The direction of the Whitacre needle aperture affects the extent and duration of isobaric spinal anesthesia. Anesth Analg 1997; 84: 337–41

Van Bogaert LJ. Lumbar lordosis and the spread of subarachnoid hyperbaric 0.5% bupivacaine at cesarean section. Int J Gynaecol Obstet 2000; 71: 65–6

Vandam LD. On the origins of intrathecal anesthesia. Int Anesthesiol Clin 1989; 27: 2–7.

Van Gessel EF, Forster A, Schweizer A, Gamulin Z. Comparison of hypobaric, hyperbaric, and isobaric solutions of bupivacaine during continuous spinal anesthesia. Anesth Analg 1991; 72: 779–84

Van Gessel EF, Forster A, Gamulin Z. Continuous spinal anesthesia: where do spinal catheters go? Anesth Analg 1993a; 76: 1004–7

Van Gessel EF, Praplan J, Fuchs T, Forster A, Gamulin Z. Influence of injection speed on the subarachnoid distribution of isobaric bupivacaine 0.5%. Anesth Analg 1993b; 77: 483–7

Van Gessel E, Forster A, Gamulin Z. A prospective study of feasibility of continuous spinal anesthesia in a University hospital. Anesth Analg 1995; 80: 880–5

Van Zundert AA, De Wolf AM. Extent of anesthesia and hemodynamic effects after subarachnoid administration of bupivacaine with epinephrine. Anesth Analg 1988; 67: 784–7.

Van Zundert AA, Grouls RJ, Korsten HH, Lambert DH. Spinal anesthesia. Volume or concentration-what matters? Reg Anesth 1996; 21: 112–8

Veering BT, Burm AG, Spierdijk J. Spinal anaesthesia with hyperbaric bupivacaine. Effects of age on neural blockade and pharmacokinetics. Br J Anaesth 1988; 60: 187–94

Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. Br J Anaesth 1981; 53: 273–8

Wildsmith JAW. Correspondence: minimum effective local anaesthetic dose for spinal anaesthesia. Br J Anaesth 2005a; 94: 865–6

Wildsmith JAW. Correspondence: minimum effective local anaesthetic dose for spinal anaesthesia. Br J Anaesth 2005b; 95: 427

Williams DA. Interval estimation of the median lethal dose. Biometrics 1986; 42: 641–5

Wetherill GB, Chen H, Vasudeva RB. Sequential estimation of quantal response curves: a new method of estimation. Biometrika 1966; 53: 493–4

Wilhelm S, Standl T; Burmeister M, Kessler G, Schulte am EJ. Comparison of continuous spinal with combined spinal-epidural anesthesia using plain bupivacaine 0.5% in trauma patients. Anesth Analg 1997; 85: 69–74

Wu CFJ. Efficient sequential designs with binary data. Am Stat Assoc J 1985; 80: 974–84

Yamashita A, Matsumoto M, Matsumoto S, Itoh M, Kawai K, Sakabe T. A comparison of the neurotoxic effects on the spinal cord of tetracaine, lidocaine, bupivacaine, and ropivacaine administered intrathecally in rabbits. Anesth Analg 2003; 97: 512–9

Yaksh TL, Noueihed RY, Durant PAC. Studies of the pharmacology and pathology of intrathecally administered 4-anilinopiperidine analogues and morphine in the rat and cat. Anesthesiology 1986; 64: 54–66

9. SUMMARY IN ESTONIAN

Lokaalanesteetikumi dooside määramine puusaliigese endoproteesimise operatsioonidel kasutades kateeterspinaalanesteesiat

Anestesioloogia areng viimaste dekaadide jooksul on tingitud uutest arusaamadest perioperatiivselt haige käsitlemisel, valu patofüsioloogia paremast tundmisest, uute ja ohutute anesteetikumide ning anesteesiameetodite juurutamisest. Regionaalanesteesia meetodite kasutamise sagedus kirurgiliste operatsioonide valutustamisel on tõusnud, sest nende kasutamise tulemusel esineb oluliselt vähem eluohtlikke tüsistusi nagu kopsuarteri trombemboolia. Samuti väheneb perioperatiivne verekaotus ning suremus. Sagedamini kasutatakse spinaalanesteesiat, mis on lihtne ja ohutu ning pikka aega kasutusel olnud anesteesiameetod. Spinaalanesteesia erivormiks on kateeterspinaalanesteesia. Selle meetodi puhul on võimalik manustada ravimit spinaalruumi asetatud kateetri abil fraktsioneeritult väikeste doosidena, mille tulemusena säilub stabiilne hemodünaamika. Operatsiooni pikenemisel on võimalik kateetri kaudu manustada ravimi lisaannuseid ning postoperatiivselt jätkata efektiivset valuravi lokaalanesteetikumide ja opioididega. Kliinilisse praktikasse on juurdumas uus spinaalkateetri süsteem ”Spinocath” (nn. kateeter nõela peal), milles spinaalkateeter on suure diameetriga ning mis võimaldab ravimi paremat segunemist spinaaruumis. Spinaalkateetrite kasutamise puhul on võimalik neuroloogiliste kõrvaltoimete (n. punktsioonijärgne peavalu) esinemine, mille esinemissagedus on väike. Kasutuselolevate (bupivakaiin) ja uute lokaalanesteetikumide (levobupivakaiin, ropivakaiin) annuste kohta kateeterspinaalanesteesias on kirjanduses andmed vasturääkivad või puuduvad. Kirjanduse andmetel on sagedamini kasutatud minimaalse lokaalanesteetikumi doosi ja kontsentratsiooni määramist ravimi efektiivse doosi hindamisel. Vastuolulised on ka andmed spinaalkateetri tipu asendi toimest spinaalanesteesia levikule.

Uurimistöö eesmärgid

Uurimistöös seati eesmärgiks anda ülevaade spinaalkateetri kasutamisest anestesioloogias, hinnata tänapäeval kasutatavate lokaalanesteekumide minimaalset efektiivset doosi ning spinaalkateetri otsa asendi toimet anesteesia levikule. Täpsustatult oli eesmärk leida vastused järgmistele küsimustele:

1. anda ülevaade spinaalkateetri kasutamisest kliinilises praktikas;
2. hinnata nn. üles- ja -alla statistilist meetodit lokaalanesteetilise efektiivse doosi määramisel;

3. määrata isobaarse levobupivakaiini ja ropivakaiini minimaalne lokaalanesteetiline doos kateeterspinaalanesteesia puhul puusaliigese proteesimise operatsioonidel;
4. määrata isobaarse bupivakaiini efektiivne lokaalanesteetiline doos kateeterspinaalanesteesia puhul puusaliigese proteesimise operatsioonidel;
5. hinnata spinaalkateetri tipu asendi toimet ibobaarse bupivakaiini efektiivsele lokaalanesteetilisele doosile.

Patsiendid ja metoodika

Kogu uurimustöö põhineb kolme eraldioleva patsiendirühma andmetel. Kateeter-spinaalanesteesia teostati ”Spinocath” kateetriga.

Esimeses artiklis on antud ülevaade spinaalkateetrite kasutamise võimalusest kliinilises töös, tuginedes 106 haigele. Hinnati anesteesiametodi efektiivsust, anesteesia levikut, haige asendi toimet spinaalkateetri tipu asendile spinaalruumis ning esinevaid probleeme.

Teises artiklis analüüsiti Dixoni, Wetherhilli ja logitanalüüsi statistilisi meetodeid, mida kasutatakse minimaalse efektiivse ravimdoosi määramisel. Analüüs viidi läbi 41 haige näitel kolmanda artikli haigetest. Täpsemalt hinnati meetodite täpsust ja kasutatavust ravimi efektiivse doosi määramisel.

Kolmandas artiklis uuriti 41 haiget puusaliigeste endoproteesimise operatsioonidel kateeterspinaalanesteesias. Määrati lokaalanesteetikumide- isobaarse levobupivakaiini ja ropivakaiini minimaalne lokaalanesteetiline doos kasutades nn. üles- ja -alla meetoodit. Hinnati isobaarse levobupivakaiini ja ropivakaiini doosi toimet anesteesia levikule ning hemodünaamika näitajatele, kirjeldati peavalu esinemissagedust.

Neljandas artiklis uuriti 48 haiget, kellel kateeterspinaalanesteesia viidi läbi isobaarse bupivakaiiniga puusaliigese endoproteesimise operatsioonidel. Määrati ravimi efektiivne lokaalanesteetiline doos. Hinnati röntgenograafiliselt kateetri tipu asendit subarahnoidaalruumis ning analüüsiti kateetri tipu asendi toimet lokaalanesteetikumi efektiivsele doosile.

Uurimistööst tulenevad järeldused

1. Spinaalanesteesia makrokateetriga on efektiivne regionaalanesteesia meetod, mis on kasutatav operatsioonidel alajäsemetel ning kõrvaltoimete esinemissagedus on väike;
2. üles- ja -alla meetod on sobilik väikeste ja väga väikeste uuringugruppide puhul. Oluline on algdoosi valik ja sammu δ suurus doosi muutmisel. Logitanalüüsi meetod on eelistatud standardse statistilise tarkvara olemasolu tõttu;
3. määratud isobaarse levobupivakaiini ja ropivakaiini minimaalne lokaalanesteetiline doos kateeterspinaalanesteesia puhul puusaliigese proteesimise operatsioonidel on vastavalt 11,7 mg ja 12,8 mg;

4. määratud isobaarse bupivakaiini efektiivne lokaalanesteetiline doos (ED_{50} ja ED_{95}) kateeterspinaalanesteesia puhul puusaliigese proteesimise operatsioonidel on 7,1 mg ja 12,3 mg;
5. kateetri tipu asend subarahnoidaalruumis ei avalda toimet isobaarse bupivakaiini efektiivse doosi suurusele.

10. ACKNOWLEDGEMENTS

The present study was carried out between 2002–2004 at the Department of Anaesthesia, Tartu University Hospital, in co-operation with the Department of Anaesthesia University of Turku, Finland.

I would like to express my sincere gratitude and appreciation to all those who have supported me, and in particular:

Prof. Klaus Olkkola for constant support and encouragement during the study.

Prof. Joukko Jalonen for continuous positive support and for sharing his knowledge on everything about writing and publishing a scientific paper. In addition, during many years he has supported the Estonian anaesthesiologists in creating contacts with Finland and in the development of the speciality.

Prof. Riku Aantaa, my academic supervisor for his constructive guidance, detailed advice and continuous support during the study.

Associate Prof. Jüri Samarütel, my teacher and mentor in anaesthesiology and intensive care, for valuable comments, support and advice during my whole working period.

Prof. Albert Van Steenberge for introducing me to the field of regional anaesthesia.

Prof. Emeritus Ain-Elmar Kaasik for positive support during the study.

Dr. Urmo Kööbi, former head of Intensive Care Unit and Tartu University Hospital for creating an optimal atmosphere during my whole working period.

Ms. Ene Käärik for tremendous help in arranging my statistical material.

All my colleagues at the Department of Anaesthesia of Tartu University Hospital for their help and friendly atmosphere.

My mother Hilja for support, understanding and encouragement.

Finally, my family Anneli, Indrek, Silver and Liisa for love and support, and for always being there when I needed it most.

11. ORIGINAL PUBLICATIONS

ISOBARIC BUPIVACAINE VIA SPINAL CATHETER FOR HIP REPLACEMENT SURGERY: ED_{50} AND ED_{95} DOSE DETERMINATION

Andres Sell, MD[1], Klaus T Olkkola, MD, PhD[2], Jouko Jalonen, MD, PhD[2], Riku Aantaa, MD, PhD[2]

[1] Department of Anaesthesia and Intensive Care of Tartu University Clinics, 8 L. Puusepp Street, 51014 Tartu, Estonia
[2] Department of Anaesthesiology and Intensive Care of Turku University Hospital, Kiinamyllynkatu 4–8, FIN-20520 Turku, Finland

Address correspondence to:
Andres Sell
Department of Anaesthesia and Intensive Care of Tartu University Clinics
51014 Tartu, Estonia
Phone: + 372 7 318320
Fax: + 372 7 318106
E-mail: andres.sell@kliinikum.ee

Background: Continuous spinal anaesthesia with spinal catheters allows incremental dosing of the local anaesthetic and, consequently, less haemodynamic change. However, little is known about the required doses. Therefore, we designed a study to assess those local anaesthetic doses of isobaric bupivacaine which were effective in 50 % (ED_{50}) and 95 % (ED_{95}) of the patients undergoing hip replacement surgery.

Methods: Forty-eight patients undergoing hip replacement surgery were randomly allocated to one of six possible groups of eight patients to receive 6, 7, 8, 9, 10 or 12 mg isobaric bupivacaine in a double-blind manner. The ED_{50} and ED_{95} values were calculated by logistic regression model. The position of the spinal catheter tip was confirmed by x-rays.

Results: The ED_{50} and ED_{95} values were 7.1 mg (95% CI, 6.0–8.4) and 12.3 mg (95% CI, 8.9–15.7). The location of the tip of the intrathecal catheter had no effect on local anaesthetic requirements. Eight patients required ephedrine after anaesthesia induction and a further 11 patients required ephedrine for correction of hypotension during surgery.

Conclusion: The observed ED_{50} and ED_{95} values may guide us to use small doses of isobaric bupivacaine for hip replacement surgery. Hypotension is still possible even though low doses of isobaric bupivacaine were used.

Keywords: Anaesthetic techniques; spinal; bupivacaine; surgery; orthopaedic.

The use of a spinal catheter technique and incremental dosing of local anaesthetic allows the use of small local anaesthetic doses without the risk of failure of the block in normal clinical practice. Previous clinical studies have compared continuous spinal anaesthesia (CSA) with conventional spinal anaesthesia, demonstrating fewer episodes of hypotension and lesser need for vasopressors (1, 2). Titration of local anaesthetic dose may thus be beneficial in the haemodynamically-compromised patient. Titrability of the extent of the block is also evident with CSA (3). One factor that may affect the local anaesthetic dose requirements, is the direction, which the catheter tip takes upon insertion. Indeed, a cranially running microcatheter has been shown to result in faster onset of analgesia and smaller dose requirements of local anaesthetic than a caudally running catheter (4). A macrocatheter system, which provides more homogenous distribution of local anaesthetic, has been commercially available for clinical practice for some time (5). We designed the present study to assess those local anaesthetic doses of isobaric bupivacaine administered via a spinal catheter which were effective in 50 % (ED_{50}) and 95 % (ED_{95}) of the patients undergoing hip replacement surgery. The study design allowed us also to evaluate the effect of macrocatheter tip position on these variables.

METHODS

After local ethical committee approval and written informed consent, 48 patients (ASA physical status I-III, aged 37–79 yr, 17 male and 31 female) scheduled for hip replacement surgery under CSA were included in this prospective, randomised, double-blinded study. Exclusion criteria included pregnancy, morbid obesity (body mass index > 35 kg m^{-2}), diabetic and other neuropathies, skin infection at the site of injection, allergy to bupivacaine and other common contraindications for spinal anaesthesia. The patients were randomly allocated to one of six possible groups to receive 6, 7, 8, 9, 10 or 12 mg isobaric bupivacaine (Marcaine Spinal®; AstraZeneca AB, Södertälje, Sweden; 5 mg/ml, with a density of 0.9994 mg ml^{-1} at 37°C) for CSA, using sealed envelopes indicating the study group the patient. The used bupivacaine solution can be considered isobaric with the cerebrospinal fluid (6). Eight patients were allocated to each dose group. The sample size was based on previous similar studies (7) and the doses were chosen based on our previous clinical experience.

To ensure that the procedure could be correctly blinded, one anaesthetist was responsible for patient randomisation and performing the spinal block, and a second anaesthetist, unaware of patient group allocation, was responsible for intraoperative and postoperative assessments and data collection. All patients were unaware of the group allotment. All blocks were performed by the same anaesthetist (AS). We used a catheter-over-needle technique for CSA. The set includes a 27-gauge Quincke type spinal needle with 22-gauge spinal catheter with a tip hole and an additional side hole at 7 mm from tip (Spinocath®; B. Braun Melsungen, Germany). First, a Crawford-type 18-gauge needle was placed in the midline at L3-4 interspace (identified by the iliac crest joining line) as cephalad as possible in the epidural space with the patient in the lateral position and the side to be operated up. Then the spinal needle with the spinal catheter over it was pushed through the epidural needle into the subarachnoid space. The catheter was inserted forward 2–2,5 cm and needles were withdrawn. The volume of 1.2 to 2.4 ml of bupivacaine was manually administered via the intraspinal catheter with an injection speed of 1 ml in 15 seconds. Twenty minutes after bupivacaine administration the following were assessed: (i) response to pinprick at T12 dermatome level on the side of surgery; (ii) response to transcutaneous tetanic electric stimulation (50 Hz at 60 mA) for five seconds at T12 level on the side of surgery; and (iii) motor function on the side of surgery assessed by modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints) (8). Anaesthesia was considered successful when there was loss of sensation to pinprick and to tetanic electric stimulation, and complete motor block. The study ended at the time when these criteria were assessed, but all drugs and adverse effects were recorded until the patient had recovered from anaesthesia. If successful clinical anaesthesia was not achieved within 20 minutes additional doses of 2–8 mg of bupivacaine, based on the extent of block and other clinical factors, were administered for surgical anaesthesia via the catheter. The sizes of the supplemental doses were not dictated by the protocol and were thus not used in ED_{50} and ED_{95} value calculations. Patient monitoring included ECG, non-invasive measurement of blood pressure at 3-min intervals and recording of peripheral oxygen saturation. Any decrease in systolic blood pressure below 90 mmHg and more than 25 % of the preoperative value was treated by attending anaesthetist with 5 mg ephedrine bolus, which was repeated until hypotension was corrected. All catheters were injected after surgery with 0.4 ml of radiopaque dye and examined by radiography for verification of their tip position. Catheter tip location was considered cranial when the tip was over the lower margin of the third lumbar vertebra and caudal when the tip was below the lower margin of the third lumbar vertebra. All patients were clinically assessed daily during the three postoperative days to determine signs of neurotoxicity and postdural puncture headache.

STATISTICS

Results are expressed as mean (SD) unless mentioned otherwise. The normality of distribution was assessed using Kolmogorov-Smirnov test. We used analysis of variance to test homogeneity of groups. Logistic regression analysis was used to estimate the ED_{50} and ED_{95} values of bupivacaine and to evaluate the possible effect of the catheter tip location to success rate of anaesthesia and bupivacaine dose requirement. Analysis was performed with use of statistical package SAS 8.2 for Windows.

RESULTS

The patient characteristics are presented in Table 1. There were no differences between the groups in terms of age, weight, height and gender. No major adverse events occurred in any of the patients. One patient had postdural puncture headache of mild severity, which was treated successfully with fluids and NSAIDs. The ED_{50} value for bupivacaine was 7.1 mg (95% CI 6.0–8.4) and ED_{95} value 12.3 mg (8.9–15.7) (Fig 1).

Anaesthesia was successful by the predetermined criteria in 32 patients. Three out of these patients needed additional local anaesthetic to complete surgery. The mean (SD) total dose of bupivacaine required to complete surgery was 10 (3.6) mg in all 48 patients. The mean duration of surgery was 118 (13) min.

The postoperative roentgenograms revealed 30 catheter tip locations in cranial and 14 tip locations in caudal position by our definition. The catheter tip position could not be visualized in four patients. Estimated by the logistic model, which includes both the dose and the catheter tip position (cranial/ caudal) factors, there was neither a statistically significant effect of catheter tip position ($p = 0.2$) nor statistically significant interaction effect of dose and catheter tip position ($p = 0.6$) to success.

The puncture level of the spinal catheter was correctly identified in 25 cases (52.1%). In five cases (10.4%) the level of puncture was lower than that estimated by the anaesthetist. The puncture level was one or two spaces higher than thought by the anaesthetist on 18 occasions (37.5%).

Eight patients required ephedrine during the first 20 min and a further 11 patients required ephedrine for correction of hypotension during surgery (cumulative dose 18 (15) mg).

DISCUSSION

This study was designed to obtain the ED_{50} and ED_{95} values of isobaric bupivacaine in an aim to find out the smallest appropriate initial local anaesthetic

dose for hip replacement surgery. The use of spinal catheter allowed supplemental dosing of the local anaesthetic in case of a failed initial block. The calculated ED_{50} and ED_{95} values of isobaric bupivacaine were 7.1 mg and 12.3 mg, respectively. We defined sufficient anaesthesia for hip replacement surgery as loss of pinprick at T12 dermatome. This definition proved suitable in this set-up with isobaric bupivacaine as only three patients out of 32 patients with initially sufficient anaesthesia required additional local anaesthetic to complete surgery. Even so, supplemental dosing of the local anaesthetic was feasible before and during surgery using the intraspinal catheter. As the supplemental doses were given according to clinical instead of protocol-defined criteria, we considered them given in too random fashion to be included in the logistic regression analysis. Nevertheless, we also calculated the mean total dose (10 mg) of bupivacaine required to complete surgery in all 48 patients. Previously, doses of 5–30 mg of isobaric bupivacaine have been reported to be required for similar surgery (9, 10).

Studies comparing fixed doses of bupivacaine in different volumes and concentrations have demonstrated that the total dose of local anaesthetic in milligrams determines the level of sensory blockade, more so than the volume or concentration (11, 12). Therefore we made no effort to make the total volumes of all doses equal, as the volume likely has no significant influence on the mean spread of the local anaesthetic in the cerebrospinal fluid. The densities of these mixtures would have also changed by diluting the local anaesthetics with different amounts of saline to obtain the same injection volume.

In addition to dose, the major determinants that affect subarachnoid spread of injected local anaesthetics and that may be used to control the level of sensory and motor blockade are baricity of the local anaesthetic and the posture of the patient (13). The effect of the site of drug injection using spinal catheters is more complex. Most anaesthetists aim to place a spinal catheter in a cephalad direction hoping to facilitate cranial spread of local anaesthetic and increase the extent of sensory blockade. A cranially directed 28-gauge end-port catheter has been shown to decrease the onset time of analgesia and the dose of isobaric bupivacaine required to achieve a sufficient sensory anaesthesia level compared to a caudally running catheter (4). Similarly, there was a correlation between the position of the catheter and the spread of sensory block using a 19-gauge end-port spinal catheter with isobaric and hyperbaric bupivacaine (14). In contrast, no correlation was found between the level of the tip and the achieved sensory level with hypobaric bupivacaine or tetracaine using a 20-gauge catheter with three side ports (15). Spinal catheters with several holes might thus allow better mixing of local anaesthetic in the cerebrospinal fluid (5). In line with these studies, we could not show any effect of the spinal catheter tip location on isobaric bupivacaine dose requirements using a 22-gauge catheter with a tip hole and an additional side hole. However, the number of patients in each dose group is may be too small to draw a definite conclusion regarding the catheter tip position effect.

It seems that the likelihood of caudal positioning of the catheter increases the longer the catheter is advanced into the intrathecal space: microcatheters inserted in patients in a lateral position and introduced more than 4 cm into subarachnoid space had a higher incidence of being placed caudally compared with for those inserted less than 4 cm (16). In addition, if directional needle for microcatheter insertion was used, a high proportion of catheters will take a cranial direction (17). The Spinocath® catheter that was used in the present study is a catheter-over-the needle system and the catheter should be advanced no more than 2–3 cm in the subarachnoid space according to the manufacturer's instructions. As most anaesthetists, we tried to insert the spinal catheter in cranial direction. In order to facilitate this, the catheter was introduced only 2–2,5 cm into the intrathecal space with the patient in the lateral position. Still, only in 68% of patients the catheter tip was in cranial position per our definition (over the lower margin of third lumbar vertebra). However, based on our result, the catheter tip position may not play a significant role after all in determining the extent of the block. We also identified the puncture level of catheter insertion using roentgenograms. The clinical judgement was correct in only approximately half of the cases, most often the puncture site was higher than expected. Previous studies have demonstrated similar success rates when attempting to identify lumbar interspaces (18).

One of the reasons to use small initial dosing of intrathecal local anaesthetics is to avoid hypotension. There is some evidence that spinal anaesthesia - induced hypotension increases the risk of myocardial ischaemia which in turn may be avoided using incremental dosing of local anaesthetics through a spinal catheter (19). We did not see any major haemodynamic adverse effects and only eight patients required ephedrine for correction of hypotension during induction of anaesthesia (i.e. the first 20 min after injection bupivacaine) as judged by the attending anaesthetist. Further doses of ephedrine were required in some patients to treat hypotension occurring in association with blood loss. We did not monitor myocardial ischaemia in a way that would allow us to discuss the relationship of ischaemia and hypotension in our patients. Nevertheless, CSA allowed us to use low doses of isobaric bupivacaine with little haemodynamic effects. Similar low incidences of hypotension have previously been reported in association with the use of low doses of bupivacaine (19, 20, 21).

Postdural puncture headache and neurotoxicity have been described following CSA with various incidences (22, 23). In the present study only one out of 48 patients experienced post dural puncture headache. None of the patients reported signs of neurotoxicity such as transient neurologic symptoms or cauda equina syndrome. Most published cases of cauda equina syndrome have been related to hyperbaric 5% lidocaine (24). The sample size of 48 patients in the present study is too small to allow us to state that isobaric bupivacaine via CSA would not be neurotoxic, either. Thus, neurological symptoms have to be examined carefully in all patients in whom CSA technique is applied until further available evidence.

In conclusion, we have shown that the observed ED_{50} and ED_{95} values may guide us to use small doses of isobaric bupivacaine for hip replacement surgery. Hypotension is still possible even though low doses of isobaric bupivacaine were used.

ACKNOWLEDGEMENT

We wish to thank Mrs. E. Käärik (Institute of Mathematical Statistics, University of Tartu) for statistical advice.

REFERENCES

1. Klimscha W, Weinstabl C, Ilias W, et al. Continuous spinal anesthesia with microcatheter and low-dose bupivacaine decreases the hemodynamic effects of centroneuraxis blocks in elderly patients. *Anesth Analg* 1993; **77**: 275–80.
2. Favarel-Garrigues JF, Sztark F, Petitjean ME, Thicoipe M, Lassie P, Dabadie P. Hemodynamic effects of spinal anesthesia in the elderly: single dose versus titration through a catheter. *Anesth Analg* 1996; **82**: 312–6.
3. Collard CD, Eappen S, Lynch EP, Concepcion M. Continuous spinal anesthesia with invasive hemodynamic monitoring for surgical repair of the hip in two patients with severe aortic stenosis. *Anesth Analg* 1995; **81**: 195–8.
4. Standl T, Beck H. Influence of the subarachnoid position of microcatheters on onset of analgesia and dose of plain bupivacaine 0.5% in continuous spinal anesthesia. *Reg Anesth* 1994; **19**: 231–6.
5. Holst D, Möllmann M, Scheuch E, Meissner K, Wendt M. Intrathecal local anesthetic distribution with the new Spinocath catheter. *Reg Anesth Pain Med* 1998; **23**: 463–8.
6. Lui ACP, Polis TZ, Cicutti NJ. Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. *Can J Anaesth* 1998; **45**: 297–303.
7. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED_{50} and ED_{95} of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology* 2004; **100**: 676–82.
8. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand* 1965; **16**(Suppl): 55–69.
9. Biboulet P, Deschodt J, Aubas P, Vacher E, Chauvet P, D'Athis F. Continuous spinal anesthesia: does low-dose plain or hyperbaric bupivacaine allow the performance of hip surgery in elderly? *Reg Anesth* 1993; **18**: 170–5.
10. Pitkänen M, Rosenberg R, Silvanto M, Tuominen M. Haemodynamic changes during spinal anaesthesia with slow continuous infusion or single dose of plain bupivacaine. *Acta Anaesthesiol Scand* 1992; **36**: 526–9.
11. Ben-David B, Levin H, Solomon E, Admoni H, Vaida S. Spinal bupivacaine in ambulatory surgery: the effect of saline dilution. *Anesth Analg* 1996; **83**: 716–20.

12. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT, Korkeila JE. Low-dose bupivacaine: a comparison of hypobaric and near isobaric solutions for arthroscopic surgery of the knee. *Anaesthesia* 1999; **54**: 540–5.
13. Hocking G, Wildsmith JAW. Intrathecal drug spread. *Br J Anaesth* 2004; **93**: 568–78.
14. Biboulet P, Capdevila X, Aubas P, Rubenovitch J, Deschodt J, d'Athis F. Causes and prediction of maldistribution during continuous spinal anesthesia with isobaric or hyperbaric bupivacaine. *Anesthesiology* 1998; **88**: 1487–94.
15. Van Gessel EF, Forster A, Gamulin Z. Continuous spinal anesthesia: where do spinal catheters go? *Anesth Analg* 1993; **76**: 1004–7.
16. Standl T, Beck H. Radiological examination of the intrathecal position of microcatheters in continuous spinal anaesthesia. *Br J Anaesth* 1993; **71**: 803–6.
17. Standl T, Eckert S, Rundshagen I, Schulte am Esch J. A directional needle improves effectiveness and reduces complications of microcatheter continuous spinal anaesthesia. *Can J Anaesth* 1995; **42**: 701–5.
18. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell R. Ability of anaesthetists to identify a marked lumbar interspace. *Anaesthesia* 2000; **55**: 1122–6.
19. Juelsgaard P, Sand NP, Felsby S, Dalsgaard J, Jakobsen KB, Brink O, Carlsson PS, Thygesen K. Perioperative myocardial ischaemia in patients undergoing surgery for fractured hip randomized to incremental spinal, single-dose spinal or general anaesthesia. *Eur J Anaesthesiol* 1998; **15**: 656–63.
20. Sutter PA, Gamulin Z, Forster A. Comparison of continuous spinal and continuous epidural anaesthesia for lower limb surgery in elderly patients. A retrospective study. *Anaesthesia* 1989; **44**: 47–50.
21. Maurer K, Bonvini JM, Ekatodramis G, Serena S, Borgeat A. Continuous spinal anesthesia/analgesia vs. single-shot spinal anesthesia with patient-controlled analgesia for elective hip arthroplasty. *Acta Anaesthesiol Scand* 2003; **47**: 878–83.
22. Mahisekar UL, Winnie AP, Vasireddy AR, Masters RW. Continuous spinal anesthesia and post dural puncture headache: a retrospective study. *Reg Anesth* 1991; 16: 107–11.
23. Horlocker TT, McGregor DG, Matsushige DK, Chantigian RC, Schroeder DR, Besse JA. Neurologic complications of 603 consecutive continuous spinal anesthetics using macrocatheter and microcatheter techniques. *Anesth Analg* 1997; **84**: 1063–70.
24. Ilias WK, Klimscha W, Skrbensky G, Weinstabl R, Widhalm A. Continuous microspinal anaesthesia: another perspective on mechanisms inducing cauda equina syndrome. *Anaesthesia* 1998; **53**: 618–23.

Table 1. Patient characteristics.

	6 mg (n = 8)	7 mg (n = 8)	8 mg (n = 8)	9 mg (n = 8)	10 mg (n = 8)	12 mg (n = 8)
Age (yr)	66.5 (56–75)	64.0 (54–79)	65.3 (60–75)	62.1 (37–73)	65.1 (44–78)	67.5 (45–75)
Weight (kg)	84.3 ± 11.6	75.5 ± 15.6	81.6 ± 22.2	76.3 ± 15.0	78.6 ± 12,2	84.3 ± 11.6
Height (cm)	168.4 ± 8.0	162.8 ± 8.3	169.7 ± 12.0	164.1 ± 11.9	168.4 ± 8.0	169.3 ± 11.8
Gender (male/female)	2/6	1/7	4/4	1/7	5/3	4/4

Values are mean (range) or mean ± SD. Data were assessed for normal distribution using Kolmogorov-Smirnov test ($p > 0.1$). There were no differences between the groups in terms of age, weight, height and gender (one-way ANOVA, $p > 0.6$).

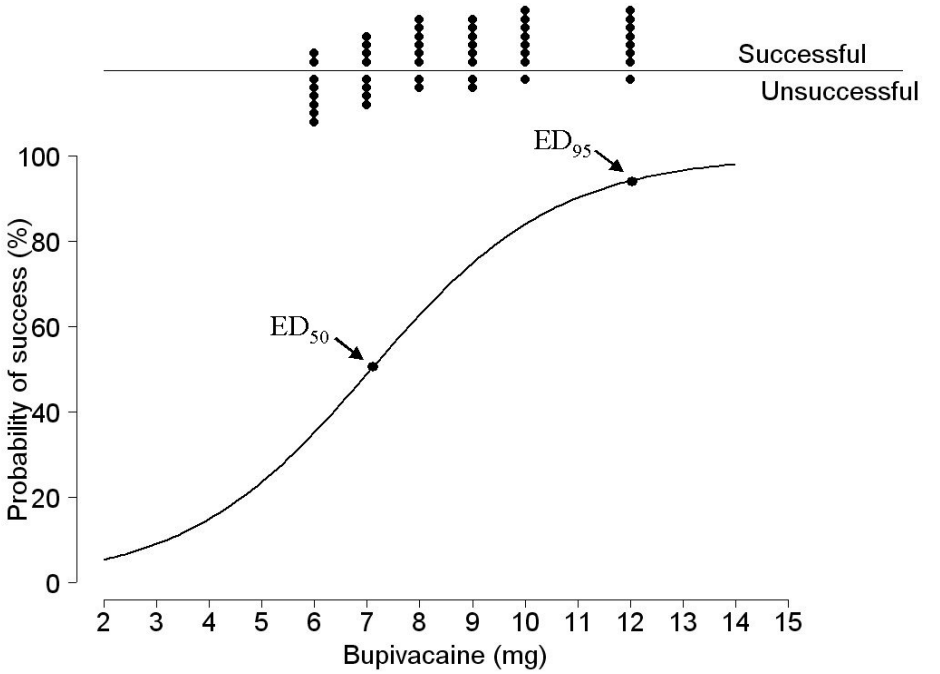

Figure 1. Logistic regression plot to determine ED_{50} (7.1 mg) and ED_{95} (12.3 mg) for isobaric bupivacaine using an intraspinal catheter.

CURRICULUM VITAE

Andres Sell

Citizenship: Estonian
Date and place of birth: 18.06.1961, Räpina, Estonia
Marital status: Married, 3 children
Address: Department of Anaesthesia of Tartu University Hospital
L. Puusepa 8, 51014 Tartu, Estonia
Tel. +372 7 318320, Fax + 372 7 318106
E-mail: andres.sell@kliinikum.ee

Education

1968–1979	Räpina Secondary School
1979–1985	University of Tartu, Faculty of Medicine
1985–1986	Internship in anaesthesiology and intensive care at Tartu University Hospital

Professional employment

1986–1988	Anaesthesiologist in Intensive Care Unit at Tartu University Hospital
1988–1990	Chief of Intensive Care Unit at Tartu University Hospital
1991–present	Chief of Department of Anaesthesia of Tartu University Hospital

Special courses in anaesthesiology and intensive care

1989	Postgraduate course at Hanover Medical High School Hospital, Germany, 1 month
1992	Postgraduate course at Homolcka Hospital, Prague, Czech Republic, 1 month
1993	Postgraduate course at Rigshospitalitet, Copenhagen, Denmark; 1 month
1996	Training course at St.Anne Clinic, Brussels, Belgium, 2 weeks
2002	Training course at Turku University Hospital, Turku, Finland; 2 weeks

Membership

1985–present	Member of the Estonian Society of Anaesthesiologists
1997–present	Board member of the Estonian Society of Anaesthesiologists
1995–present	Board member of the Estonian Pain Society
1997–present	Member of the European Society of Regional Anaesthesia
2005	Member of the European Society of Anaesthesiologists

Scientific work

Research field:
Regional anesthesia, monitoring in anaesthesia, difficult airway management, acute postoperative pain management, safety in anaesthesia.
33 scientific publications.

ELULOOKIRJELDUS

Andres Sell

Kodakondsus: Eesti
Sünniaeg ja -koht: 18.juuli 1961, Räpina, Eesti
Abielus, 3 last
Aadress: Pootsmani 36, Tartu 51017, Eesti
Telefon: 372 7318320, faks 372 7 318106
E-mail: andres.sell@kliinikum.ee

Haridus ja erialane täiendus

1968–1979	Räpina Keskkool
1979–1985	Tartu Ülikooli Arstiteaduskond, ravi eriala
1985–1986	Tartu Ülikooli Arstiteaduskond, anestesioloogia ja intensiivravi internatuur
1989	Hannoveri Meditsiinikõrgkooli Kliinik, Saksamaa, 1 kuu
1992	Praha Homolcka Kliinik, Tšehhi Vabariik, 1 kuu
1993	Kopenhaageni Rigshospitalitet, Taani, 1 kuu
1996	Brüsseli St.Anne Kliinik, Belgia, 1 kuu
2002	Turu Ülikooli Haigla, Soome, 2 nädalat

Erialane teenistuskäik

1986–1988	Maarjamõisa Haigla intensiivravi osakonna arst
1988–1990	Maarjamõisa Haigla intensiivravi osakonna juhataja
1990–1991	Maarjamõisa Haigla intensiivravi osakonna arst
1991–1995	Maarjamõisa Haigla anestesioloogia ja operatsiooniosakonna juhtaja
1995–1999	Maarjamõisa Haigla anestesioloogia osakonna juhataja
2000– käesoleva ajani	SA TÜK Anestesioloogia ja intensiivravi kliiniku üldanestesioloogia osakonna juhataja, vanemarst- õppejõud

Teadustegevus

Peamiseks uurimisvaldkonnaks on regionaalanesteesia erivormid- kateeter-spinaalanesteesia, kombineeritud spinaal- ja epiduraalanesteesia; tüsistused regionaalanesteesias, regionaalanesteesia ohutus; valuravi (äge postopera-

tiivne); laste ja täiskasvanute ambulatoorne anesteesia; monitooring anesteesias ja raske hingamistee käsitlus. Avaldatud teaduslike publikatsioonide üldarv 33.

Erialaseltsid

1985 Eesti Anestesioloogide Seltsi liige
1997 Eesti Anestesioloogide Seltsi juhatuse liige
1995 Eesti Valu Seltsi juhatuse liige
1997 Euroopa Regionaalanesteesia Seltsi (ESRA) liige
2000 Tartu Arstide Liidu liige
2005 Euroopa Anestesioloogide Seltside Assotsiatsiooni (ESA) liige